Wisconsin Medical Journal

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PREVENTION:
the patient's role

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COVER THEME
Prevention: The patient's role

With spring upon us—whether it seems like it or not—the seasonal problems of sunburn and sinuses aren't far behind. This Wisconsin Medical Journal *includes articles that focus on some of these issues and the role patients can play in prevention of related health conditions.*

Cover design by Mary Kay Adams-Edgette.

The mission of the *Wisconsin Medical Journal* is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

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Sinuses, sunburn, and prevention

John J. Frey, III, MD
Medical Editor, Wisconsin Medical Journal

Spring has sprung… And can allergies and sunburns be far behind? Articles in this issue of the *Wisconsin Medical Journal* look at some of the things that clinicians will be addressing in the coming months, assuming the snow melts before June. Both asthma and allergies seem to be increasing in prevalence in recent times. Most seasonal allergies do not result in extrinsically induced asthma but cause a large use of over the counter (OTC) medications and visits to physician offices. The burden of allergic rhinitis in the United States may even be higher than suspected.[1] Rabago and colleagues have found evidence that sinus irrigation may present symptomatic relief for allergic rhinitis and decrease asthma symptoms as well (Nasal irrigation for chronic sinus symptoms in patients with allergic rhinitis, asthma and nasal polyposis: a hypothesis generating study. *WMJ*. 2008;107(2):17). If their hypotheses are true, the medication-related side effects of many of the OTC medications could be avoided, cost of care lowered both for asthma and allergic rhinitis, and patients themselves be able to better prevent or decrease symptoms. The article includes some information about the use of this "alternative" but effective therapy which, at some point, may go from an alternative to treatment of choice.

Years ago, the American Cancer Society used to advertise "Fight cancer with a checkup and a check," creating one of the most successful campaigns not only for raising awareness of symptoms that might indicate risk of cancer but also to raise money for cancer research. In their article in the *Journal* on the relationship of nonmelanotic skin cancers and patients' willingness to change preventive behaviors, Rhee and colleagues found that patients did change their behaviors about skin cancer prevention. However, these same patients did not change behaviors to decrease their risk for other preventable causes of cancer (Behavior modification and risk perception in patients with nonmelanoma skin cancer. *WMJ*. 2008;107(2)10). Many physicians believe that seeing a patient for cancer might offer a teachable moment for education about many other health behaviors. But the reality, based on the data from Rhee et al appears to be that patients are more resistant to behavior change than we hoped. We shouldn't give up trying, but continued reinforcement by both consultant and primary physician might be necessary.

While we are mentioning prevention, the review article by Bandi and colleagues on approaches to recurrent urolithiasis offers a primer for clinicians on various types of stones and their etiology (Practical approach to metabolic evaluation and treatment of the recurrent stone patient. *WMJ*. 2008;107(2):39). Prevention of recurrent stones relies heavily, again, on patient adherence to dietary and other behaviors that we know will lessen the likelihood of recurrence. Anyone who has had a kidney stone or treated a patient who has had one would have difficulty imagining that anyone would want to run the risk of developing another. However, as in the patient's with nonmelanoma skin cancers, patients—for whatever reasons—may not believe that their personal likelihood of recurrence is high enough to change their ways of living. Perhaps a second stone might make the point better than our advice.

Finally, as AIDS has become a chronic disease rather than a universally fatal one, testing to detect HIV infection needs to be expanded to find patients early and decrease the likelihood, despite decades of instruction about high risk behaviors, that HIV infection spreads in the population. However, as Petroll and colleagues point out, there are currently inconsistencies between guidelines for testing from the Centers for Disease Control and medical practice in Wisconsin (Updated CDC guidelines for HIV testing: a review for Wisconsin practitioners *WMJ*. 2008;107(2):32). Altering the guidelines would require legal changes as well as changes in physicians' behavior. Often, particularly when faced with the history of the stigma and significant negative consequences associated with even testing for HIV in the not- too-distant-past, generalized testing would require physicians to change our behaviors. We can be as difficult in that regard as our patients.

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Studying the physician patient relationship: A 21st century approach

Shaili Jain, MD

Several authors have noted that genuine medical professionalism is in peril and the negative impact of this on the doctor-patient relationship is noticeable, with the American public becoming "suspicious and distrustful of, and even antagonistic to the profession."[1-3] Numerous academic and public articles draw attention to waning public trust in their relationship with their doctor, with charges that doctors are self-serving, greedy, and impersonal.[4] More than one-third of patients in the United States experience dissatisfaction with hospital care. Of the small number who actually complain, they report perceived disrespect, disagreement about expectations of care, inadequate information, distrust, perceived unavailability, interdisciplinary miscommunication, and misinformation.[3,5]

This "rift" in the doctor-patient relationship is problematic. The Institute of Medicine's first simple rule to improve the quality of health care is a long-term healing relationship.[6] If there is a rift in the doctor-patient relationship, how is it possible for there to be a healing relationship, and how can quality health care be delivered?

The exact problems in the doctor-patient relationship and how they are being solved has received little scientific study. Medical literature discusses what a "good doctor" should be,[2,7-8] but surprisingly, there is little evidence on what patients think makes a good doctor.[9-10] I suspect that the rift may be more a matter of miscommunication. Ironically, patients who are dissatisfied with him or her often do not confront their doctor, but simply find another doctor. Therefore, most doctors may not have an accurate idea of their patient's opinions of them[5] and do not have a source of objective feedback from patients.

There is hope that a large-scale scientific study of the current state of the doctor-patient relationship (with input from both sides) would fill a gap in the existing body of medical knowledge.

On-line Web logs (frequently modified Web pages in which dated entries are listed in reverse chronological order) are becoming popular vehicles for personal expression.[11-12] Mainstream media has commented on the grassroots power of blogs and their potential for possessing socially transformative and democratizing potential.[12] Medical and health care-related weblogs have begun to punctuate cyberspace with content ranging from personal stories by health care professionals to current medical news and industry developments.

Bedside Manner (www.bedsidemanner.com) is a research weblog that invites patients and physicians to share their experiences with a specific focus on what is being done right in the doctor-patient relationship and how to improve the doctor-patient relationship. It is a 21st century approach to studying a complex relationship; ease of access, complete confidentiality, and transparency of communication are the basis for its foundation. It literally enables physicians and patients to get on the same page.

The patient's voice is already being heard on other Web sites, where they are rating their experiences with doctors (naming names) and whether the experience was good or bad. The time has come for physicians to publicly ask the vital question, "what do patients think makes a good doctor?" and solicit the answer directly from those doctors who have taken an oath to serve. Only when we have this data can we take confident steps to ensure an excellent, trusting doctor-patient relationship reassumes its rightful place as the most important piece in optimal health care delivery.

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What a piece of work is man: The Body Worlds exhibit at the Milwaukee Public Museum

Joan M. Bedinghaus, MD, FAAF; Seth L. Foldy, MD, MPH, FAAFP

Already viewed by more than 20 million people worldwide, the Body Worlds exhibit is currently on display at the Milwaukee Public Museum until June 1, 2008.

The creator of the exhibit, Gunther von Hagens, MD, has patented a technique, which he calls "plastination," for impregnating cadavers and anatomical specimens with plastic or silicone rubber. Plastination not only preserves the prosected bodies, but enables the posing of the bodies in unusual ways.

The Body Worlds exhibit is beautiful and fascinating. In the first room, most of the exhibits are fairly conventional: human bodies displayed standing, dissected to display muscles, ligaments, and the nervous system. The nervous system dissections are beautifully detailed, evoking envy in those of us who remember struggling to delineate the brachial plexus as first-year medical students. In the main hall of the exhibit, the bodies are displayed in poses that are both spectacular and, to some, disturbing.

The exhibit claims an educational mission, and some of the posed bodies clearly demonstrate that goal. For example, a body posed as a leaping martial artist also displays a dozen kinds of orthopedic hardware and prosthetic joints. The hand of "The Smoker" retains the familiar nicotine-stained finger while casually holding a cigarette, humanizing the black-stained lungs that otherwise might be less meaningful emotionally. Accompanying cross-sections that contrast emphysematous lungs with normal lungs are dramatic, though not well explained to a lay audience. "Obesity Revealed" is a cross-section of a body with a 5-inch layer of subcutaneous fat. Whether its ugliness will motivate anyone to control their weight is an open question.

The dissection and mounting of "The Longitudinally-Expanded Body" emphasize the concentric circles of corporeal organization from muscle to bone to internal organs, providing some insight into the functionality of this design. In "The Runner," centrifugal force is emphasized by the arrangement

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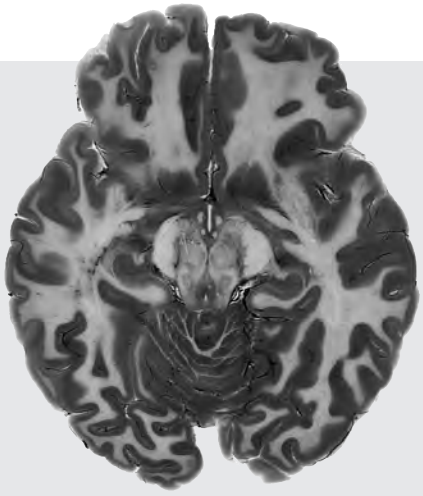
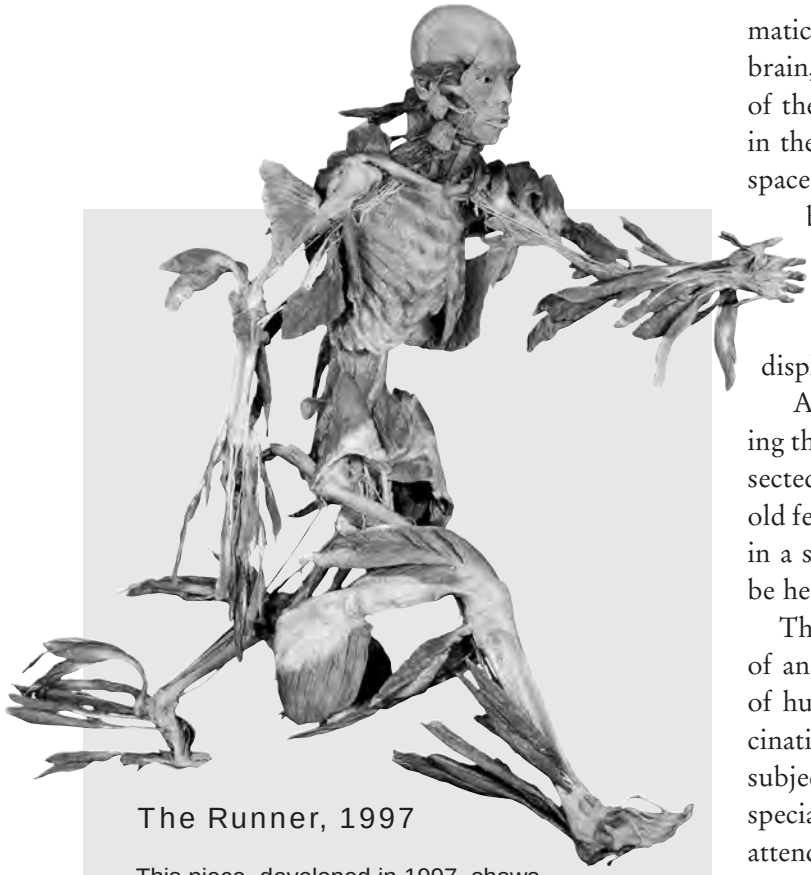


Horizontal slice of the brain

A horizontal slice through the cerebrum provides a clear image of the darker and lighter portions of the brain. The darker portion in the image is the gray matter and basal ganglia while the lighter portion is the white matter of the brain. This image also demonstrates the furrowed surface of the brain, with numerous convolutions and recessions. Only one-third of the surface of the brain is visible, while the other two-thirds is hidden in the grooves.



The Runner, 1997

This piece, developed in 1997, shows the skeletal and muscular systems in use while running. In order to show both systems, the muscles are detached from the bones and folded back or drawn out, demonstrating how intricately the muscles are attached to the bones to provide such mobility. As a whole-body plastinate, "The Runner" can be seen from any angle at the exhibit, allowing viewers the opportunity to see these muscles in action from a variety of perspectives.

of muscles flying off from each hand, arm and leg, revealing more muscle anatomy than a conventional dissection could. But while it emphasizes the dynamic forces of movement, it does not aid in understanding the leverage and balance of opposing forces that control locomotion.

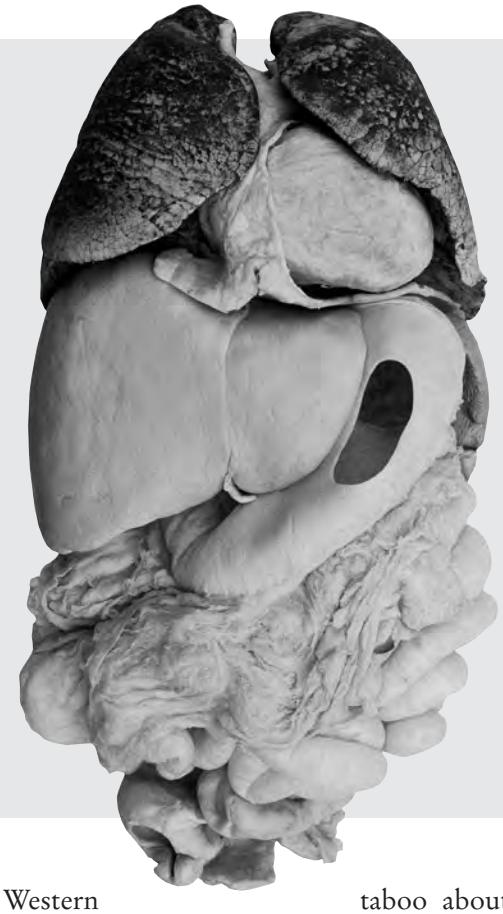
By sheer size, "The Rearing Horse with Rider" dominates the room. The horse's muscles and tendons are displayed; the rider's skeleton is separated from his muscles so that it looks like 2 riders. The rider holds the horse's brain in one hand and his own brain in the other. Several other bodies are gracefully posed as athletes. "The Basketball Player" is particularly dramatic. It is mounted as though lurching forward. The brain, which is barely contained in the halved bowl of the skull, mimics the barely controlled basketball in the hand. Both appear on the verge of flying into space. The display emphasizes the dynamic forces on both external and internal organs (brain, hand). Even if these cadavers were not dissected, the audacity of the mounting would be evident. At this point the spectacle and challenge of the display overshadow their educational purpose.

A display that includes a series of fetuses showing the sequence of prenatal development and the dissected body of a pregnant woman with her 8-month-old fetus in utero is set off from the rest of the exhibit, in a special curtained area where soft, sad music can be heard.

The exhibit also includes material on the history of anatomic dissection. It reveals that the dissection of human cadavers has been a subject of public fascination and controversy for as long as it has been a subject of scientific inquiry. During the Renaissance, special theaters were built in which dissections were attended by hundreds of curious paying customers. The Body Worlds display includes an 18th century illustration that shows a beautiful young woman looking back over her shoulder, with a sensuously curved back. What appears at first glance to be an elaborately pleated scarlet gown are the muscles of her back, dissected and splayed, with her dorsal root ganglia running next to her spine like a string of pearls. Thus, Body Worlds is continuing an artistic tradition of beautiful, and sometimes disturbing, anatomical art.

The Controversies

The Body Worlds exhibits (there are now 4 touring collections) and their creator, Gunther von Hagens, MD, have generated a great deal of controversy as well as interest. Doctor von Hagens has patented the plastination process and currently operates a multi-million dollar business in Dalian, China, in which several hundred human cadavers are dissected and preserved each year, for exhibitions as well as for use in health profession training. The procurement of bodies is one source of controversy, with periodic accusations that the bodies of mental patients and executed prisoners have been acquired without appropriate consent. Dr von Hagens denies these accusations, and to date they have not been legally proven. In 2004, the California Science Center set up a commission that confirmed



Thoracic and Abdominal Organs in their Usual Configuration

The lungs display massive deposits of tar (smoker's lungs).

Plastination of the internal organs allows viewers a glimpse behind the ribs, to see the detailed and complex inner workings of the body. This piece shows the lungs, heart, diaphragm, liver, stomach, spleen, greater omentum, small intestines, bladder, and prostate gland. Perhaps the most eye-catching part of this plastinate is the black color of the lungs, which give an undeniable image of the mass deposits of tar on the lungs from smoking.

Doctor von Hagens's claim that all bodies exhibited in Body Worlds were those of donors who gave informed consent.

The aesthetic excitement and daring that make the exhibit so attractive are also the source of another controversy: Is the display of human remains a violation of human dignity? Such displays are usually deemed acceptable for educational purposes, but when the educational aspects are overshadowed by entertainment value, they transgress social norms.

Some of these controversies were the subject of discussion by members of the Milwaukee Academy of Medicine, who were able to tour the exhibit without other museum patrons present February 18. The Academy's evening at the exhibit included a select group of docents uniquely qualified to comment on these issues as well as the content of the exhibit. They included medical ethicist Arthur Derse, MD, JD; medical anthropologists Paul Brodwin, PhD, and Michael Oldani, PhD; forensic anthropologist Peter Killoran, PhD; orthopedic surgeon Jim Steele, MD; psychiatrist Carl Chan, MD; and forensic pathologist Russell Alexander, MD.

In his introductory remarks, Dr Brodwin recommended that observers evaluate von Hagens's own statements about his purposes: "To break down the Western taboo about the encounter with death … [by providing] an opportunity to contemplate death without grieving and physical revulsion … with no odor of decay or formaldehyde … freed from the taint of disgust." However, the exhibit, by posing the bodies in action (with glass eyes open) seems to avoid perceiving these individuals as dead.

Based on his own observations of attendees at the exhibit, Dr Brodwin suggested another reason for the exhibit's drawing power: "People come to participate in the democratization of medicine… democratic processes promise transparency… [Body Worlds is] redrawing the boundary between the specialized knowledge of medicine and general knowledge."

He observed spectators relating the contents of the exhibit to their own experiences: "That's what my artificial knee looks like," or "Those are the muscles I use when I'm working out."

"Transparency" seems an especially appropriate term for this exhibit. Its immense popularity demonstrates that people today, just like those who crowded the dissecting theatres of the Renaissance, still have a strong human desire to transgress the boundary of the skin and to see what's inside the body, with all its weirdness and beauty.

WISCONSIN MEDICAL JOURNAL

Behavior Modification and Risk Perception in Patients with Nonmelanoma Skin Cancer

John S. Rhee, MD, MPH; Melinda Davis-Malesevich, MD; Brent R. Logan, PhD; Marcy Neuburg, MD; Mary Burzynski, RN; Ann B. Nattinger, MD, MPH

ABSTRACT

Context: Nonmelanoma skin cancer (NMSC) is the most common cancer among humans, yet risk perceptions and preventive health behaviors in those who survive this cancer are relatively unknown.

Objectives: To assess the impact of the disease and its treatment on sun-protective behaviors, general preventive health behaviors, and risk perception in NMSC patients, and to determine factors associated with behavioral change.

Design and Setting: A prospective study was conducted of 211 consecutive NMSC patients presenting to a dermatologic surgery clinic at a tertiary care university medical center from February 2005 to March 2006. These patients were all adults, were fluent in English, and had NMSC of the head and neck. Of the 211 eligible patients, complete data was obtained for 183 (87%). The most common reasons for dropout were voluntary withdrawal and incompletely answered surveys.

Intervention and Outcome Measures: Surveys that assessed disease-specific quality of life (QoL), preventive health behaviors, sun-protective behaviors, and risk perception were administered before and after surgical treatment of NMSC.

Results: Sun-protective behaviors improved post-surgery even after controlling for seasons ($P<0.001$). Predictor factors associated with increased sun-protective behavior included poor skin tanning ability, summer season, no employment, less comorbid conditions, and previous NMSC treatment. Baseline QoL was not predictive of behavioral change. As for risk perception, respondents thought they were more likely than someone similar to themselves to develop future NMSCs but thought they had similar risks of developing melanoma or other non-skin cancers ($P<0.001$).

Conclusions: NMSC patients demonstrated disease-specific behavior modifications by selectively improving their sun habits but showed no significant improvement in other preventive health behaviors. This finding is consistent with patients' specific perception of increased risk for future NMSCs, but surprisingly, not for melanoma. Increased patient education of associated cancer risks with NMSC is warranted.

INTRODUCTION

Skin cancers are the most common malignancies in human beings, accounting for approximately 50% of all cancers. The American Cancer Society estimates there are at least as many nonmelanoma skin cancer (NMSC) cases diagnosed each year as all other cancers combined (more than 1 million cases per year).[1] Exposure to UV light is the primary risk factor associated with NMSC. The likelihood of individuals to participate in sun-protective behaviors (wearing protective clothing, avoiding the sun, using sunscreen, and skin self-exams) is associated with other behaviors of a healthy lifestyle.[1]

Epidemiologic evidence has suggested that NMSC patients are at risk for not only future NMSCs, but also for developing other malignancies, such as cancers of the buccal cavity, salivary glands, and lungs, as well as lymphoma, leukemia, and melanoma.[2-6] The shared risk factor—UV light exposure—is thought to be the causal link for a 3-fold increase in the risk for malignant melanoma for NMSC patients.[4] However, the association between NMSC and other noncutaneous malignancies—15%-30% higher than expected compared to the general population—remains more perplexing in its causal link and remains a controversial topic.[5,7]

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In addition, although NMSC is not life-threatening, the disease has been shown to negatively impact patients' quality of life (QoL).[8-9] Given the conspicuous location of NMSC lesions, issues related to disfigurement, depression, anxiety, and embarrassment have all been shown to be relevant for NMSC patients.[9] The fear of developing future cancers and the effect of the disease and/or its treatment on social interactions and body image may motivate patients to undertake strategies of primary cancer prevention such as sun-protective behaviors, smoking cessation, improving diet, and other preventive health behaviors.

In the context of this potential vulnerability, we wanted to assess the current state of cancer risk perception and participation of general preventive health behaviors in this patient population, and to determine if risk perception or behavior would change following treatment of NMSC. Furthermore, we hypothesize that NMSC patients would be more likely to change their sun-protective behavior following treatment of their skin cancer and that baseline disease-specific QoL would be a significant predictor for behavioral change.

METHODS

The study period—consisting of enrollment, treatment, and follow-up—spanned 13 months (February 1, 2005 to March 2006). The sample included 211 patients who had biopsy-proven NMSC and were referred to a dermatologic Mohs surgery clinic at the Medical College of Wisconsin. All participants were of sufficient physical and mental capacity, were adults, and were fluent in written and spoken English. Participants with major psychiatric illnesses or cognitive impairment were excluded. Of the 211 eligible patients, complete data was obtained for 183. The most common reasons for dropout were voluntary withdrawal and incompletely answered surveys.

At the initial visit, a trained research nurse explained the research study to the participants and obtained an Institutional Review Board-approved informed consent. All enrolled participants completed the survey before interaction with the physician. Surveys were administered again at a 4-month follow-up appointment, with participants completing the survey prior to interaction with the physician. The 4-month endpoint was chosen because this was when the majority of the postoperative healing process has finished—ie, it was possible to evaluate the "final" postoperative result. If the patient was not able to make the scheduled appointment, the survey was sent with a self-addressed stamped envelope to a home address. Three attempts were made to contact the participant to fill out the follow-up survey.

Measures

Demographic, clinical, and sun-protective behavioral information was collected. Demographic variables included age, gender, marital status, education level, and socioeconomic status (employment and income). Clinical variables included type of cancer, location of lesion, number of different locations, histology, previous treatment, existence of comorbid conditions, and reconstruction technique (Table 1).

Each patient completed the survey before and after surgery. The survey measured patient perception of risk (3 questions), general preventive health behaviors (5 questions), sun-protective behaviors (5 questions), and other sun habits and perceptions (5 questions). Review of the literature and clinically relevant questions led to the survey's contents. Responses were recorded on a 5-point Likert scale. Baseline QoL was assessed using the Skin Cancer Index (SCI), a recently validated disease-specific instrument for patients with NMSC.[8] The SCI is a 15-item, disease-specific QoL instrument with 3 subscales—emotional, social, and appearance. The SCI total score was used as the predictor variable, with potential analysis of the subscale scores pending significance of the total score.

Data Analysis

For the sun-protective behavior questions, Cronbach's alpha was computed, along with item total correlations and correlations between any 2 questions. This determined whether the questions reasonably formed an instrument describing the characteristic in aggregate. Sun-protective behaviors of patients were use of sunscreen, avoiding the sun during peak hours, seeking shade, wearing a hat, and wearing sun-protective clothing. A univariate comparison of pre- and post-surgery outcomes was performed using the paired t-test for each question. *P*-values were computed using the paired t-test. Multivariate analysis was performed using mixed models for repeated measures data, with several between-subject factors and 1 within-subject factor of time (2 levels: pre- and post-surgery). Between subject factors included demographic factors (age, employment, gender, marital status, educational attainment, income), clinical factors (location of lesion, reconstructive technique), QoL as measured using the SCI, skin tanning ability, and the season at which the survey was completed. Assumptions of mixed models including normality of sampling distributions and homogeneity of

Table 1. Descriptive Data for Sociodemographic and Medical Characteristics

Variable Level	N	%
Overall	183	–
Gender		
Female	93	51
Male	90	49
Race		
Caucasian/White	182	99
American Indian/Aleut/Eskimo	1	1
Age Median (63) Range (21-85)		
≤65	95	52
>65	88	48
Education		
High school or less	46	25
Vocational school or some college	48	26
College degree	57	31
Professional or graduate degree	32	17
Marital Status		
Married/Live-in partner	140	77
Other	43	23
Income		
≤$50,000	61	33
>$50,000	113	62
Missing	9	5
Job Status		
Full-time	67	37
Part-time	18	10
Self-employed	14	8
Retired	63	34
Homemaker	16	9
Other	5	3
Location of Lesion		
Nose	56	31
Lips	16	9
Eyelid	23	13
Ears	18	10
Cheek	25	14
Forehead	18	10
Temple	11	6
Neck	1	1
Scalp	7	4
Other	29	16
Histology		
Basal	164	90
Squamous	16	9
Other	3	2
Previous Treatment		
None	115	63
Same site/recurrent	23	13
Other site	45	25
Comorbidity		
Present	154	84
Absent	29	16

variance-covariance matrices were checked and deemed adequate. Least squares estimates of means for main effect variables (no interaction with time) were provided with 95% confidence intervals, and a *P*-value testing the main effect. For variables having significant interaction with time, least squares estimates of means and 95% confidence intervals were calculated both pre- and post-surgery for each level of the variable.

RESULTS

The median age was 63 years, with a range from 21 to 85. Gender was split almost evenly: 93 females (51%) and 90 males (49%). Basal cell carcinomas were found in 90% of the sample (n=164), squamous cell carcinomas were detected in 9% (n=16), and 2% (n=3) had other types of lesions. More lesions (n=104) were located on the nose (56 patients [31%]), cheek (25 patients [14%]), and eyelid (23 patients [13%]) than other areas of the face, neck, or scalp. Other descriptive statistics for participants' demographic and clinical characteristics are shown in Table 1.

Responses to questions measuring perceived risk of developing cancer were consistent both pre- and post-surgery (Figure 1). On average, respondents rated the likelihood of developing another basal or squamous skin cancer within the next 10 years compared to someone of the same age, race, and gender to be "somewhat likely." Patients revealed their perceived chance of developing a melanoma to be "about the same" as someone of similar demographics. Likewise, patients thought their risk for developing a non-skin cancer was "about the same." However, patients expressed belief that they were at higher risk for developing another NMSC compared to other cancers ($P<0.001$). For all 3 risk perception questions, there was little change in pre- and post-surgery responses in the univariate analysis, indicating that, in general, patients retained the same view of their personal risk of developing cancer.

Collectively, sun-protective behaviors significantly improved following surgery ($P<0.001$) (Table 2). The 5 sun-protective behavior questions, as an aggregate, demonstrated reasonable internal reliability (Cronbach's alpha=0.7, pre-surgery and post-surgery). Therefore, the aggregate score was used as the marker of sun-protective behavior for the univariate and multivariate analyses.

In the univariate analysis (Table 3), among the preventive health behaviors, only the participation in self-exams for skin cancer appeared to be significantly increasing post-surgery ($P<0.001$). In the multivariate analysis, predictor factors associated with increased

sun-protective behavior included poor skin tanning ability, summer season, no employment, less comorbid conditions, and previous NMSC treatment (Table 4). More specifically, participants who were not in the workplace had similar sun-protective behavior before surgery compared to those who were employed. However, those participants who were not employed demonstrated greater positive change in their sun-protective behavior. Also, participants who had no previous NMSC had significantly poorer baseline sun-protective behavior scores. This trend continued even after surgery, but the gap closed to some degree.

Baseline mean (confidence interval) SCI total score was 68.3 (65.2, 71.4). When baseline SCI total score was included as a predictor variable in the multivariate analysis for sun-protective behaviors, it was not significant either as a main effect (P=0.632) or as a predictor variable comparing before and after treatment (P=0.556).

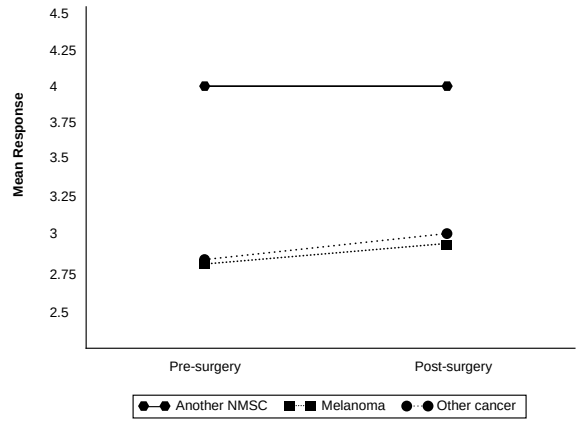

Figure 1. Chance of developing NMSC, melanoma, or other cancer within the next 10 years. Mean response of 182 respondents to the following questions: Within the next 10 years how likely would you rate your… chance of developing another skin cancer (basal or squamous); chance of developing melanoma; and chance of developing another type of cancer (breast, lung, etc.)? Responses were measured on a scale of 1 to 5, where 1 = "very unlikely", 2 = "somewhat unlikely", 3 = "about the same", 4 = "somewhat likely", and 5 = "very likely".

DISCUSSION

We have demonstrated that NMSC patients improve sun-protective behaviors after surgery but show little change in non sun-related preventive health behaviors, some of which may be putting them at risk for other cancers. Although NMSC patients in this study received no specific counseling on sun exposure or skin cancer prevention, they exhibited a significant increase in post-surgical use of sunscreen, hats, and sun-protective clothing. This finding is consistent with past studies.[10-12] Additionally, they were more likely to stay in the shade, avoid the sun during peak UV emissions, and they increased the frequency of post-surgical skin self-exams. These behavioral changes are consistent with the risk perceptions of this patient cohort and the Health Belief Model.[13] The Health Belief Model indicates that a health behavior change is more likely in individuals who perceive themselves to be at risk for a health problem, perceive the consequences of the illness to be severe, perceive many benefits to carrying out preventative actions, and perceive few barriers to assuming these actions.

Certain demographic and clinical factors were identified that correlated with greater compliance or change in sun-protective behavior. Patients who were previously treated for NMSC reported significantly greater pre- and post-surgery participation in sun-protective behaviors as compared to patients treated for the first time. Although first-time NMSC patients also showed significant improvement in their sun habits following surgery, previously treated patients showed more improvement. This suggests that patients with prior history of NMSC perceived themselves to be at higher risk for skin cancer than first-time NMSC patients, which likely motivated them to further change harmful sun-related behaviors. The higher risk perception by these patients is corroborated by studies that have demonstrated an increased risk for future NMSCs. In a meta-analysis from 2000, it was estimated that the average proportion of patients developing a subsequent basal cell carcinoma or squamous cell carcinoma within 3 years was 44% and 18%, respectively.[2] Additionally, the risk for a subsequent NMSC has been shown to be strongly associated with the number of previously diagnosed NMSCs.

Along with previous treatment, absence of any comorbid conditions also correlated with increased sun-protective behaviors. It is possible that patients with other comorbid conditions were less likely to improve their sun habits because they were more concerned with medical conditions other than NMSC.

Employed patients were less likely than those who were retired, homemakers, or unemployed to partake in sun-protective behaviors following surgery. There are a few possible explanations for this finding. First, people in the workforce tend to be younger than retirees, who make up 75% of unemployed patients in this study. Previous studies have shown that younger patients (age 15-45) are less likely to engage in skin cancer prevention than older adults.[14] Second, employed patients tend to find themselves in social situations more often than their

Table 2. Sun-Protective Behaviors Before and After NMSC Treatment[a]

	Pre-surgery		Post-surgery		
Variable	**Mean**	**SD**	**Mean**	**SD**	***P*-value**
Sunscreen use	3.16	1.47	3.34	1.38	0.087
Limit time in sun 11 AM–3 PM	2.79	1.34	3.33	1.34	<0.001
Shade	3.10	1.16	3.34	1.10	0.007
Hat	3.26	1.43	3.56	1.37	<0.001
Protective clothing	2.73	1.23	3.10	1.24	<0.001
Total	15.01	4.47	16.65	4.37	<0.001

[a] Mean response of 182 respondents to the following questions: Within the past month how often have you… regularly used sunscreen; limited your time in the sun from 11 a.m. to 3 p.m.; stayed in the shade; wore a hat; and worn long-sleeved or other sun-protective clothing? Responses were measured on a scale of 1 to 5, where 1 = "almost never", 2 = "seldom", 3 = "sometimes", 4 = "often", and 5 = "almost always".

Table 3. Preventive Health Behaviors Before and After NMSC Treatment[a]

	Pre-surgery		Post-surgery		
General Health Behaviors	**Mean**	**SD**	**Mean**	**SD**	***P*-value**
Skin self-exams	2.81	1.27	3.14	1.18	<0.001
Alcohol consumption (reverse coded)	3.26	1.09	3.31	1.08	0.340
Tobacco use (reverse coded)	4.63	1.00	4.65	1.00	0.514
Exercise	3.54	1.24	3.51	1.32	0.700
Healthy diet	3.86	0.86	3.81	0.91	0.362

[a] Mean response of 182 respondents to questions about the frequency of participation in the following: skin self-exams; alcohol consumption; tobacco use; exercising at least 3 times per week; and eating a low-fat, high fiber diet. Responses were measured on a scale of 1 to 5, where 1 = "never", 2 = "seldom", 3 = "sometimes", 4 = "usually", and 5 = "always".

unemployed counterparts, and the societal endorsement of tanned skin as "healthy" and "attractive" has been shown to be an important motivating factor for seeking a tan and ignoring skin cancer warnings.[15]

Surprisingly, NMSC patient risk perceptions of developing future melanomas were low and did not change following treatment. A recent study revealed that the risk of NMSC patients developing cutaneous melanoma within 4 years were on average 3.45%, which is notably more than the incidence in the US general population during that same 4-year period (0.0152%).[3] NMSC patients in this study exclusively perceived themselves at higher risk for future NMSCs, not for melanoma. Despite the fact that sun exposure is the most preventable risk factor for both melanoma[16] and NMSC, patients do not seem to draw this connection. It appears that patients consider melanoma differently than NMSC and do not perceive themselves at greater risk. This finding points to a need for targeted counseling and better education of this patient cohort that is at higher risk for melanoma. Furthermore, perhaps a broader education of the public of the link between these 2 types of skin cancers is warranted.

Disease-specific QoL as measured by the Skin Cancer Index (SCI) was not predictive of behavior changes following surgery. Patients who associated NMSC with poorer QoL were expected to have greater risk perception and thus exhibit greater change in behavior; however this was not found to be the case. QoL showed no correlation with changes in sun-protective behaviors. It may be concluded that risk perception is not appreciably influenced by disease-specific QoL and that these 2 outcomes, though possibly overlapping to some degree, are essentially measuring different concerns and dimensions.

There was no significant post-treatment change in general preventive health behaviors unrelated to sun exposure, such as tobacco use, alcohol consumption, exercise, and diet. In a previous study, we demonstrated that NMSC patients who smoked did not quit smoking after treatment, but they were not any less likely to adopt sun-protective behaviors.[10] Maser et al[11] also reported no significant change in general preventive health measures in a similar group of skin cancer patients. Though perhaps not as well known by the public or among health care professionals, studies have reported the

Table 4A. Predictors of Main Effects for Sun-Protective Behaviors

Main Effects	Level	Mean (CI)	*P*-value
Skin tanning ability	Slope	-0.9 (-1.4, -0.3)	0.001
Season	Spring	15.7 (14.7, 16.8)	0.004
	Summer	17.1 (16.0, 18.1)	
	Fall	16.1 (15.1, 17.1)	
	Winter	15.6 (14.4, 16.7)	

Least square estimates of means for main effect variables (no interaction with time) are provided with 95% confidence intervals (CI), and a *P*-value testing the main effect.

Table 4B. Predictors of Interactions with Time for Sun-Protective Behaviors

Variable	Level	Pre-surgery Mean (CI)	Post-surgery Mean (CI)	*P*-value
Employed				0.004[a]
	No	14.8 (13.6, 16.1)	18.4 (17.2, 19.6)	<0.001[b]
	Yes	14.7 (13.6, 15.7)	16.6 (15.5, 17.6)	0.001[b]
	P-value[c]	0.823	0.003	
Comorbid conditions				0.003[a]
	No	14.2 (12.4, 15.9)	18.1 (16.5, 19.8)	<0.001[b]
	Yes	15.4 (14.7, 16.1)	16.9 (16.1, 17.6)	<0.001[b]
	P-value[c]	0.170	0.153	
Previous treatment				0.021a
	None	13.4 (12.3, 14.4)	16.8 (15.8, 17.8)	<0.001[b]
	New site/recurrent	16.1 (14.9, 17.4)	18.2 (16.9, 19.4)	0.002[b]
	P-value[c]	<0.001	0.036	

For variables having a significant interaction with time, least squares estimates of means and 95% confidence intervals (CI) are provided both pre- and post-surgery for each level of the variable.
[a] The *P*-value testing for interaction.
[b] A *P*-value testing for changes over time is presented for each level of the variable.
[c] A *P*-value testing for differences between levels of the variable is presented for both pre- and post-surgery.

incidence of a second malignancy (both skin and non-skin) in NMSC patients is 15%-30% higher than that of the general population.[7,17] A recent study examining this correlation in Canadian patients found comparable results.[3] Also, numerous studies have demonstrated that patients with an NMSC history are at an increased risk of cancer mortality.[18-20]

It appears that patients do not see the link between NMSC and other cancers, and their reported behaviors reflect this perception. This does raise some interesting questions for health care professionals and public health officials. In a disease as prevalent as NMSC, there is an opportunity to educate and motivate behavioral change in a potentially "vulnerable" patient population. The evidence linking melanoma and NMSC appears to be strong, and education about the shared risk factors and encouragement for skin examination appears to be warranted. Our study findings indicate that patients do need further education about the link between the 2 skin cancer types.

Frisch et al,[7] in their study of basal cell cancer patients, concluded that although the increase in absolute risk for noncutaneous cancer did not appear large enough to justify general screening for noncutaneous cancers, certain symptoms and signs relating to possible other cancers should be taken seriously in young patients who have had basal cell cancer. However, it is less clear how best to convey to patients this potential link between NMSC and non-skin cancers from a preventive health standpoint. The associated risks of non-skin cancer mortality have been described, but potential interventions that could alter the outcome have not been studied. The opportunity to change risk perceptions and motivate preventive health behavior must be weighed against the potential negative mental and emotional health sequela when describing to patients this reported associated risk. Future interventional studies are needed that incorporate general preventive health counseling and education of NMSC patients to measure the effect of these interventions in changing risk perception and behavior while measuring potentially adverse effects of this line of counseling.

Some limitations of this study must be noted. First, these data were derived from patients' self-reported par-

ticipation in behaviors. Actual patient behaviors may differ from what is being reported by the patients. Also, our cohort consisted almost exclusively of Caucasian Midwesterners. Racial and ethnic differences in sun habits have been previously reported,[21-22] and future studies should include a larger geographic area with a more diverse patient population. Furthermore, we did not include a comparison cohort; it may be interesting to compare risk perceptions and behaviors of NMSC patients to patients with other cancers as well as to individuals without cancer. Finally, a cohort of patients with greater disease severity (larger cancers, squamous cell histology, underlying immunosuppression) or less severity (basal cell cancers not needing Mohs surgery) may potentially prove to have different risk perceptions and preventive health behaviors.

CONCLUSIONS

NMSC patients are willing to improve sun-protective behaviors following surgery, and we have described certain factors that may predict higher likelihood of greater participation. However, NMSC patients do not perceive an increased risk for melanoma or for other non-skin cancers. Although patients change their sun-protective behaviors following surgery, they do not alter other potentially unhealthy aspects of lifestyle. Additional studies are needed to explore the potential impact of counseling or education about the link between NMSC and melanoma and other non-skin cancers.

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Nasal Irrigation for Chronic Sinus Symptoms in Patients with Allergic Rhinitis, Asthma, and Nasal Polyposis: A Hypothesis Generating Study

David Rabago, MD; Emily Guerard, BS; Don Bukstein, MD

ABSTRACT

Background: Rhinosinusitis is a common, expensive disorder with a significant impact on patients' quality of life. Chronic sinus symptoms are associated with allergic rhinitis, asthma, and nasal polyposis. Saline nasal irrigation is an adjunctive therapy for rhinosinusitis and sinus symptoms. Prior studies suggest that hypertonic saline nasal irrigation (HSNI) may be effective for symptoms associated with allergy, asthma, and nasal polyposis.

Objective: To assess the degree to which subjects using nasal irrigation for chronic sinus symptoms also reported improvements in symptoms related to allergy, asthma, or nasal polyposis.

Design: Qualitative study using in-depth long interviews of 28 participants in a prior qualitative nasal irrigation study. All participants were receiving daily nasal irrigation.

Results: Transcripts of interviews were systematically examined. Twelve of 21 subjects with allergic rhinitis spontaneously reported that HSNI improved symptoms. Two of 7 subjects with asthma and 1 of 2 subjects with nasal polyposis reported a positive association between HSNI use and asthma or nasal polyposis symptoms. Transcript content was organized into themes that included: (1) HSNI resulted in improvement of allergic rhinitis and asthma symptoms, and (2) HSNI should be used for symptoms of allergic rhinitis.

Conclusions: This hypothesis-generating study offers qualitative evidence that suggests patients with frequent rhinosinusitis and daily sinus symptoms, symptoms of concomitant allergic rhinitis, asthma, or polyposis may improve with HSNI. The parent studies offer strong evidence that HSNI is an effective adjunctive treatment for symptoms of chronic rhinosinusitis. Larger prospective studies are needed in patients with these diagnoses.

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INTRODUCTION

Rhinosinusitis is a common, expensive disorder that has a significant impact on patients' quality of life (QoL).[1] In a subset of patients, sinus symptoms can become chronic and are epidemiologically associated with asthma,[2-3] allergic rhinitis,[4-5] and nasal polyposis,[6] though the etiological relationships are not well understood. Each condition is associated with significant morbidity, cost, and impact on QoL.[1,7] Allergic rhinitis affects 20-40 million persons annually in the United States,[8] is responsible for 3.5 million lost-work days each year, 2 million missed school days each year,[9] and an estimated 28 million days of restricted activity or reduced productivity.[10] Total costs of allergic rhinitis have been estimated at $250 million in 1998 dollars ($291.6 million 2002 dollars).[11] Overall health care costs for allergic rhinitis are rising at a rate of 12% each year.[12] Treatment of allergic rhinitis is expensive and has significant side effects, which result in an expense of $3.8 billion alone.[13]

Hypertonic saline nasal irrigation (HSNI) is an adjunctive therapy for rhinosinusitis and sinus symptoms.[14] It flushes the nasal cavity, facilitating the evacuation of potentially allergen- and irritant-containing mucus (Figure 1).[15] It is a commonly used therapy in Wisconsin; a recent study of 286 family physicians who use HSNI found that 95% use some form of nasal saline for a variety of conditions including chronic rhinosinusitis (91%), acute upper respiratory infections (URI) (80%), allergic rhinitis (70%), irritant rhinitis (48%), and URI-triggered asthma (9.1%) (David Rabago, MD, unpublished data, 2007). Nasal saline

Figure 1. Nasal irrigation technique.

Table 1. Open-Ended Questions Used to Frame the Qualitative Interviews

1. What were your sinus problems like before using nasal irrigation and how did nasal irrigation affect you?
2. Did you experience any problems from using nasal irrigation?
3. How did you fit nasal irrigation into your life?
4. Did you get any reactions about using nasal irrigation from those around you?
5. How do you feel about nasal irrigation now?
6. What was the informational meeting like for you?
7. Is there anything else you'd like to tell us about your experience with nasal irrigation or this study?

irrigation has also been used for decades as post-operative care for endoscopic sinus surgery patients and as a complement to chronic nasal steroid use (oral communication with co-author, Bukstein) in patients with allergic rhinitis. One study of nasal saline delivered as a spray reported that it may prevent viral URI,[16] but another reported that it may not lessen the severity or duration of active URI.[17] HSNI was recently identified as "an important component in the management of most sino-nasal conditions" that is "effective and underutilized."[18] The Cochrane Collaboration has reported that HSNI is an effective adjunctive therapy for chronic rhinosinusitis symptoms.[19]

Ten randomized controlled trials (RCTs) suggest that HSNI is a safe, effective, and tolerable therapy for rhinosinusitis and chronic sinus symptoms that results in improvement in disease-related QoL scores and surrogate measures in adults and children.[20-29] A recent study reported that nasal irrigation was effective in pediatric allergic rhinitis.[30] In a closely monitored 6-month RCT,[28] and an 18-month follow-up study by this study's lead author,[31] subjects using daily 2% HSNI for chronic sinus symptoms reported improved QoL, high patient satisfaction, decreased antibiotic and nasal spray use, and improved sinus symptoms. A subsequent qualitative study of 28 subjects confirmed these findings and described the overall experience of initiating and maintaining successful HSNI use;[32] subjects felt empowered to self-treat and manage their sinus conditions, reported rapid and long-term QoL improvements, identified significant barriers to using HSNI, and acknowledged positive aspects of HSNI training and patient education about in-home use to overcome such barriers.

During the qualitative interviews,[32] several subjects spontaneously reported that HSNI improved symptoms associated with their baseline allergic rhinitis, asthma, or nasal polyposis. Because epidemiological and pathophysiological relationships between these conditions and sinus symptoms exist, and HSNI was incidentally noted to improve symptoms associated with these conditions, we speculated that HSNI might function as adjunctive therapy for these conditions. Therefore we re-analyzed qualitative data to explore the research question "Do subjects using HSNI for chronic sinus symptoms, who also reported diagnoses of allergic rhinitis, asthma, or nasal polyposis, spontaneously report improvements in symptoms related to allergic rhinitis, asthma, or nasal polyposis?"

METHODS

The methods of the parent RCT and follow-up studies (Phases 1-3) were previously reported.[28,31-32] The current study, Phase 4 (Figure 2) was approved by the University of Wisconsin Health Sciences Center Human Subjects Committee. The inclusion criteria of Phase 1 were 2 or more episodes of acute rhinosinusitis, or 1 or more episodes of chronic rhinosinusitis per year for the prior 2 years, and a "moderate to severe" daily QoL burden associated with sinus symptoms. Intervention subjects in Phases 1 and 2 used 2% buffered saline solution daily for 6 months and as needed for up to 18 months (Figure 1).[29] In Phase 3, subjects participated in a qualitative study. In-depth long interview methodology suggests that a sample size of 20-30 subjects from a larger group of subjects with similar experiences captures all or nearly all relevant data.[33] Accordingly, 28 Phase 1 and 2 subjects were interviewed to determine themes associated with HSNI use (Table 1, Figure 2). The inclusion criterion for the current study (Phase 4) was participation in the Phase 3 study.[32] Phase 3 transcripts were re-analyzed for the current study from May to July 2006 using 2 methods. First, a computerized keyword search located descriptors of asthma, allergic rhinitis, and nasal polyposis (Table 2). Second, each transcript was manually evaluated by the second author (Guerard) for phrases that were relevant to the

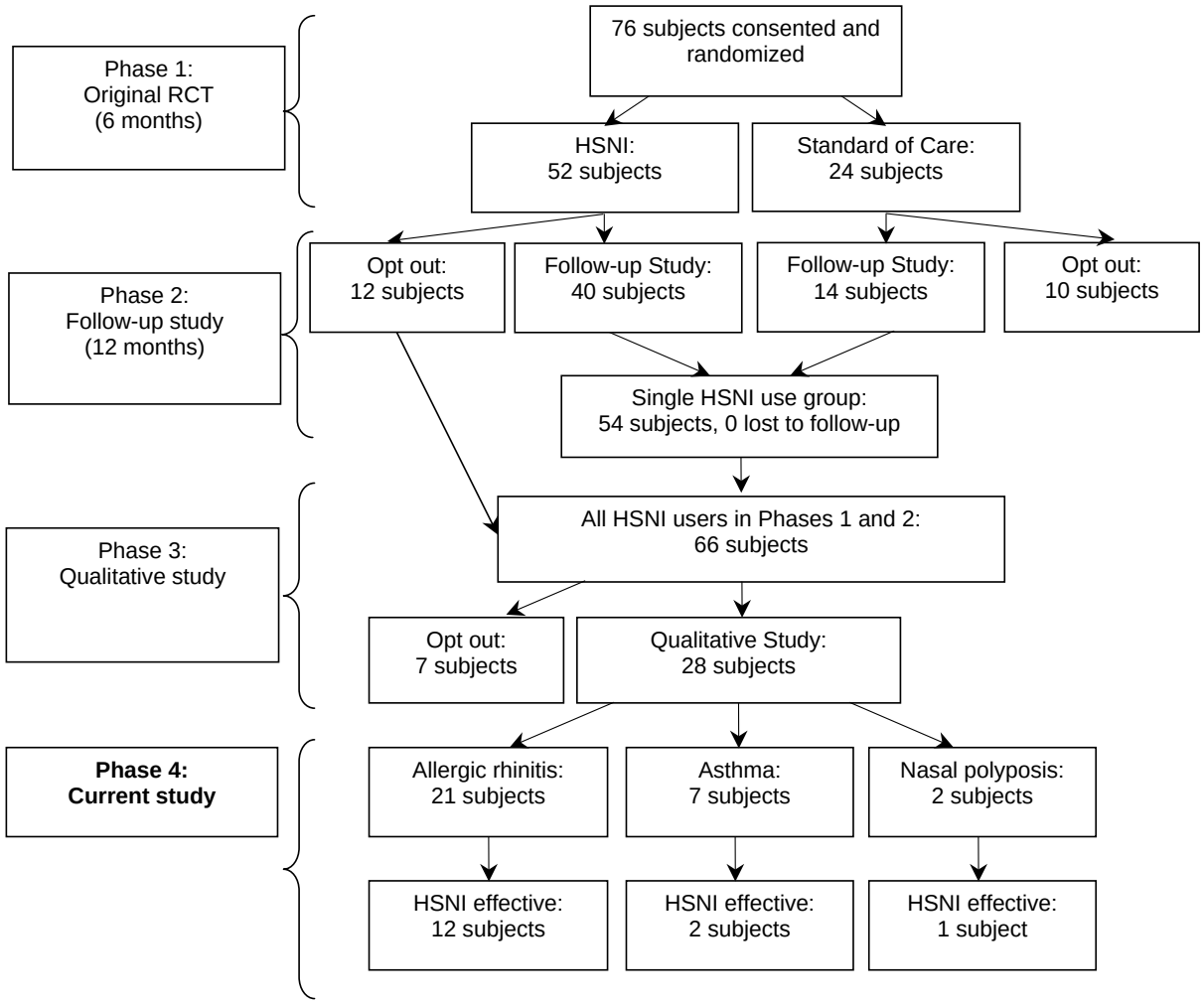

Figure 2. Subject participation in Phase 1 randomized controlled trial, Phase 2 follow-up study, Phase 3 qualitative study, and the current study (Phase 4). Note: Phase 4 subject number is >28 because some subjects had more than 1 diagnosis. HSNI=hypertonic saline nasal irrigation.

conditions of interest. Quotations from the qualitative study describing the perceived effect of HSNI on allergic rhinitis, asthma, or nasal polyposis symptoms were organized thematically.

RESULTS

Transcripts from the qualitative interviews of all 28 participants were examined. Subjects reported having allergic rhinitis (n=21), asthma (n=7), or nasal polyposis (n=3) at the beginning of Phase 1; 15 subjects reported associations between HSNI and the conditions of interest. Twelve of 21 subjects (57%) with allergic rhinitis spontaneously reported improvements in their allergic rhinitis symptoms. Two of 7 (29%) subjects with asthma and 1 of 2 (50%) subjects with nasal polyposis reported a positive association between HSNI use and asthma or nasal polyposis symptoms respectively. The age, gender, and sinus-related QoL scores of the 12 subjects with allergic rhinitis (Table 2) and of the 3 subjects with asthma or nasal polyposis were statistically similar to both the 28-member qualitative cohort and the cohort of all HSNI users in the parent study. All comments reflected a positive relationship between the subjects' use of HSNI and their perception of its effect on the conditions of interest (Table 3). Listed comments (Table 3) were distinct and separate from reports on sinus symptoms. The quotations illustrate participants' range of experience. The overall positive reaction to HSNI in the current study is consistent with that of the prior qualitative study from which this sample is drawn.[32] The comments reflect subjects with a debilitating condition (chronic sinus symptoms) who were introduced to a non-intuitive therapy whose mastery required work and insight (performing HSNI), who achieved therapeutic success (improved QoL, symptom scores), and who perceived a relationship

Table 2. Key Words Used During Computerized Keyword Search of the Interview Transcripts[a]

Asthma	Allergic Rhinitis	Nasal Polyposis
Asthma	Allergic rhinitis	Nasal polyposis
Wheeze	Allergy	Nasal
Short of breath	Seasonal allergy	Polyp
Breathing problem	Allergic	Surgery
Cough	Runny nose	
Inhaler	Itchy eye	
Albuterol	Watery eye	
	Sneeze	
	Pollen	
	Mites	
	Mold	
	Smoke	
	Decongestant	
	Antihistamine	

[a] All words were searched for as a wildcard.

between HSNI and their underlying conditions.

The most dramatic set of comments were about the use of HSNI by subjects with allergic rhinitis. Of the 21 subjects in the qualitative study with allergic rhinitis, 12 (57%) spontaneously reported improved allergy symptoms such as watery itchy eyes and rhinitis, and improved quality of life with use of HSNI. Two major themes were identified in relation to allergic rhinitis and HSNI use.

Symptom Improvement

Subjects reported improvement of symptoms associated with allergic rhinitis with HSNI use. Most subjects did not differentiate allergy symptoms, referring to them collectively as "allergy symptoms," though some identified rhinitis and watery, itchy eyes as specific symptoms. Participants reported that use of HSNI improved their allergy-related rhinitis symptoms separate from sinusitis symptoms. For example: "I am surprised that not only has my sinus incidence gone down but my whole allergy incidence has gone down," and "[nasal irrigation] helps with my sinus but it helps with my allergies as well." They also reported improved QoL, noting "just bringing [the allergen] in the house would trigger an allergic reaction and I would be miserable for days. But now [since nasal irrigation, that] doesn't even bother me," and "…we did a lot of work in a basement with a lot of mold and [then] I actually had some bad allergic reactions. [Nasal irrigation] has helped a lot. Thinking back, my allergies aren't as bad using [nasal irrigation]." "It's such a big change when you can enjoy things that people take for granted" and "[nasal irrigation] literally changes a great aspect of my life."

Two subjects related use of HSNI to asthma symptom improvement, one of whom reported "…I noticed the neti pot helps with the [asthmatic] breathing too." One subject commented on a possible preventive relationship between HSNI and nasal polyposis by stating "And then I … had [sinus surgery] again because my sinuses were so bad I was growing polyps in my nasal cavity … If I had [nasal irrigation] earlier I wouldn't have gone through what I have gone through … if I would have had a way to prevent this outside of surgery I would have done anything."

HSNI Use Recommendation

During the qualitative interview, subjects were asked to indicate the conditions for which HSNI could/should be recommended. Without prompting, 8 of 21 participants with allergies spontaneously indicated that HSNI should be used for allergy symptoms. Typical comments were: "…I think if [patients complain] about their allergies that's enough [to use HSNI]," and "I think somebody who had a lot of … allergies [should use it]. It would seem to me this would be the first line of attack for allergies."

DISCUSSION

This study investigated the relationship between HSNI use and symptoms of allergic rhinitis, asthma, and nasal polyposis in adult subjects. More than half of subjects with self-reported chronic sinus symptoms and concurrent allergic rhinitis spontaneously reported positive effects of HSNI on allergy symptoms as distinct from chronic sinus symptoms, suggesting that HSNI may be effective adjunctive therapy for allergic rhinitis. This is the first study to report such a relationship in adults. The current study adds to prior data from the same cohort[32] by suggesting that symptoms of both conditions are improved by HSNI. These results are consistent with the findings of a small but methodologically strong pediatric study;[30] patients with laboratory confirmed, pollen-triggered allergic rhinitis reported that, compared to antihistamine alone, antihistamine plus HSNI resulted in significant improvement in allergy symptom scores and reduction in antihistamine use.[30] These results are also consistent with current practice of family physicians in Wisconsin, many of whom use HSNI for allergic conditions (David Rabago, MD, unpublished data, 2007).

Two of 7 subjects with asthma reported that HSNI improved their asthma symptoms. No study has formally tested HSNI as adjunctive treatment for asthma in patients with sinus disease. Epidemiological evidence

Table 3. Baseline Demographic and Sinus-related Outcome Scores, and Post-treatment Scores

Characteristic	Phase 1 and 2 HSNI Users (N=66)	Phase 3 Qualitative Study (N=28)	Phase 4 Subjects w/Allergy Symptoms (N=21)	Phase 4 Subjects HSNI/Allergy Relationship (N=12)
Age	42.4 + 1.3	44.8 + 1.8	46.5 + 2.0	44.2 + 1.2
Female	48 (73%)	19 (68%)	15 (71%)	9 (75%)
Baseline RSDI[b]	58.8 + 1.8	57.2 + 2.9	52.5 + 3.1	56.1 + 4.9
End RSDI	77.9 + 1.8	80.1 + 2.9	76.8 + 3.4	75.8 + 5.5
Baseline SIA[c]	3.95 + 0.12	4.02 + 0.20	4.21+ 0.24	3.96 + 0.36
End SIA	2.36 + 0.13	2.29 + 0.18	2.33 + 0.19	2.42 + 0.26

[a] HSNI=hypertonic saline nasal irrigation.
[b] RSDI=Rhino Sinusitis Disability Index.[44] Using a 30-item validated multidimensional disease-specific assessment instrument, participants scored their sinus symptoms, where 0 = maximal impact of sinus symptoms on quality of life, and 100 = no impact.
[c] SIA=Single-item assessment. Using a 1-7 Likert scale where 1 = "no impact" and 7 = "maximal impact," participants responded to the statement: "Please evaluate the overall severity of your sinus symptoms since enrolled in the study."

suggests that the conditions are related; 80%-90% of children and adolescents with asthma also have nasal symptoms, and half of all patients with asthma have radiographic evidence of sinusitis, though imaging results are non-specific.[6] Whether the 2 conditions are causally linked is unclear, but in 1 study, aggressive treatment of sinusitis with HSNI with and without antibiotics resulted in significantly decreased bronchial hyperresponsiveness compared to baseline.[3] In addition, some authors have hypothesized that systemic inflammatory processes underlying asthma and allergic rhinitis are similar.[5] Studies of patients with both asthma and allergic rhinitis reported that effective treatment of allergic rhinitis results in reduced severity or frequency of asthma,[34-35] suggesting that HSNI may have a role as adjunctive therapy for allergy-induced asthma.

One subject in the current study suggested that nasal polyposis, a sequela of chronic rhinosinusitis, might have been prevented by nasal irrigation if used early enough. While speculative, at least 3 randomized controlled studies report symptomatic effectiveness of HSNI for chronic sinusitis or chronic sinus symptoms without documented polyposis.[23-24,28] Given that polyposis is an extreme form of chronic sinus disease, and that HSNI may improve the function and health of the nasal mucosa, aggressive treatment with HSNI may inhibit progression of chronic rhinosinusitis to a polypoid form.

The mechanism of nasal irrigation's effect is not well understood and is likely multifaceted. Relating HSNI mechanistically to allergic rhinitis, asthma, or polyposis is therefore somewhat speculative. However, nasal irrigation has been reported to have several physiological effects that individually, or together, may result in an improved ability of the nasal mucosa to reduce the pathologic effects of inflammatory mediators and other triggers of allergic rhinitis, asthma, and other chronic mucosal reactions. These effects include: (1) direct cleansing effect by the saline as it thins and removes obstructive mucus and crusts;[36-38] (2) removal or reduction of inflammatory mediators such as histamine, prostaglandins, leukotriennes, and eosinophil-released major basic protein;[15,39] (3) improved mucociliary function in the presence of hypertonic saline[40] and normal saline.[41] Optimal tonicity and pH of the irrigating solution are unclear.[42-43]

Limitations of this study include its small size, potential reporting bias given the prolonged contact with study personnel, and recall bias. Details of subjects' views about the effects of HSNI on the conditions of interest are limited by the fact that subjects were not specifically queried about these conditions, but rather spontaneously reported their views. Diagnoses were not obtained objectively; subjects provided medical diagnoses and effect of HSNI on symptoms of particular diagnoses by self-report. Strengths include comprehensive training in the use of nasal irrigation (film, live demonstration, demonstrated proficiency), strong continuity with subjects through 3 prior studies of varied methodologies, demonstrated effectiveness of nasal irrigation in each of these studies using a variety of outcome measures, demonstrated high subject adherence and retention, and effective data collection throughout the study. Randomized controlled studies are needed to assess the clinical effect, side-effect profile, and economic impact of HSNI in subjects with clear diagnoses of allergic rhinitis, asthma, and nasal polyposis.

CONCLUSIONS

This hypothesis-generating study suggests that patients with frequent rhinosinusitis, daily sinus symptoms, and concurrent allergic rhinitis may benefit from adjunc-

Representative Themes and Quotations About Hypertonic Saline Nasal Irrigation (HSNI) and Effects on Symptoms of Allergy Rhinitis, Asthma, and Nasal Polyposis

Theme - Allergy

Participants reported decrease in allergy symptoms and an increase in quality of life.

"I'm allergic to a lot of stuff, ragweed and pollen, and I live in a rural area where there is lots of farm and haying and that stuff goes on all summer and it was miserable for me. I am surprised that not only has my sinus incidence gone down but my whole allergy incidence has gone down. I don't know what it is, but I feel like I have more tolerance to being outside. I don't have hay fever like I had before or the runny nose and eyes and itching."

"It [HSNI] literally changes a great aspect of my life. For instance, I couldn't mow my lawn because the grass, it would just kill me. And planting flowers, …I love flowers. Planting my flowerbeds was just terrible, I would just have hay fever and then I'd be plugged up and then I'd have to go to the doctor and get more antibiotics."

"[My kids would say] 'Mom I got you flowers' and just bringing [them] in the house would trigger an allergic reaction and I would be miserable for days. But now it doesn't even bother me. I am out there picking weeds and doing a lot of stuff. I have talked to my friends about this a lot because it's a big change for me. When you suffer for a chronic illness for so long and then you don't have problems with it anymore I think it's such a big relief and I can't explain it, it's such a big change where you can enjoy things that people take for granted."

"We did a lot of work in a basement with a lot of mold and… a week or 2 after that … I actually had some bad allergic reactions and then I got an infection shortly after that too. [HSNI] has helped a lot. Thinking back, my allergies aren't as bad using the neti pot."

"What I do find is that it helps with my allergies. It helps with my sinus but it helps with my allergies as well."

"…With my allergies it's helped. I don't know if that's supposed to be or not but it's helped me cope with my allergies…"

Participants recommended HSNI for allergic symptoms when asked to name conditions for which HSNI might be useful.

"I think if [patients complain] about their allergies that's enough. There's enough other things out there that you can't help and [HSNI] seems to help."

"I think somebody who had a lot of sinuses and allergies [should use it]. It would seem to me this would be the first line of attack for allergies."

"Allergies and sinus problems."

Theme - Asthma

Patients noted less frequent asthma symptoms.

"Whereas I use the Flovent after the first couple of weeks, I was also using it [nasal irrigation] PRN and I use it twice a day now so that may be making some difference there too. I noticed the neti pot helps with the breathing…"

Theme - Nasal Polyposis

One participant speculated that HSNI might have prevented the need for surgery for nasal polyposis.

"If I would have known about HSNI 12 years ago I [might] never have had my first sinus surgery … my sinuses were so bad I was growing polyps in my nasal cavity ... If I had this [HSNI] earlier I [might not] have gone through what I have gone through."

Note: Bracketed words are the authors' interpretation of the subject's original intent; they are used to link ideas or abbreviate wordiness. Neti pot = a pot specially designed for HSNI (shown in Figure 1).

tive treatment with HSNI, and that HSNI deserves further study as adjunctive treatment for this common condition, ideally in a population without other forms of rhinosinusitis. Given that HSNI is effective, safe, inexpensive, and well-tolerated for symptoms of chronic rhinosinusitis, clinicians can feel comfortable recommending HSNI to their patients who also have allergic rhinitis. The relationship between HSNI and symptoms associated with URI-induced asthma and nasal polyposis is unclear but is likewise deserving of further study in populations with these disorders.

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WISCONSIN MEDICAL JOURNAL

What's New in Clinical Pharmacology and Therapeutics

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ABSTRACT

The US Food and Drug Administration (FDA) has approved several new drugs in the past 2 years. This article provides an overview of some of the newer drugs that are likely to find wider use in the future. The drugs reviewed in this article can be used to treat cardiovascular system problems, diabetes mellitus, multiple sclerosis, hepatitis B infection, hyponatremia, Parkinson's disease, rheumatoid arthritis, pain, constipation, and insomnia. Another drug discussed can be used to help a patient stop smoking. The article also discusses Gardasil, the recombinant vaccine against human papilloma virus (types 6, 11, 16, and 18).

INTRODUCTION

Several new drugs have been approved by the US Food and Drug Administration (FDA) in the last 2 years. The following is a summary of some of the newer agents that are likely to find wider use in treatment of various disorders in the next few years. The article refers to the safety of these drugs in pregnancy based on toxicity to the fetus in animal and human studies. Category A drugs are safe to use in pregnancy, B are probably safe, C are probably unsafe, D are unsafe, and X are definitely contraindicated. Not all drugs have been studied to assign a risk category.

The newly marketed drugs tend to be more expensive, particularly when they have a unique mode of action and their rare side effects take awhile to manifest. In general, the newer drugs should be used only if established drugs are ineffective or not tolerated by the patient.

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Studies comparing newer drugs with older, well-established drugs, particularly generic drugs, are initially hard to come by as the pharmaceutical manufacturers are reluctant to support such studies, lest their product proves inferior to the comparison drug. Eventually, comparison studies are performed by interested investigators and the comparative advantages and disadvantages of various drugs are determined.

Only 1000-3000 subjects are required in a trial to establish a drug's efficacy and seek the FDA's approval. Rare side effects that occur only once in 10,000 patients manifest after the drug is on the market and prescribed in millions of patients. If the drug causes serious or fatal toxicity, it is withdrawn from the market. Sometimes a manufacturer may withdraw the drug if it doesn't sell enough to justify continued marketing.

CARDIOVASCULAR SYSTEM

Ranolazine (Ranexa)

Ranolazine is a first selective late sodium current inhibitor approved for the treatment of chronic stable angina. It is the first new anti-anginal drug in more than 20 years. The inhibition of late sodium current results in a reduced intracellular sodium and calcium overload during myocardial ischemia. This causes inhibition of fatty acid oxidation and increases glucose oxidation generating more adenosine triphosphate (ATP) for each molecule of oxygen consumed and may decrease oxygen demand while maintaining myocardial contractility. It should be used in combination with other anti-anginal drugs such as beta-blockers, nitrates, or amlodipine as its effect may compliment the action of existing anti-anginal agents.[1] Ranolazine has been shown to be effective in increasing exercise treadmill test duration, with or without conventional anti-anginal treatment, in patients with chronic angina. The clinical benefit is consistent in patients with comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, low heart rate or blood pressure, prior myocardial infarc-

tion, or revascularization. It does not lower blood pressure and heart rate. The common adverse effects include dizziness, headache, constipation, and nausea.[2]

Ranolazine has several drug interactions. It can increase the QT interval, a measure of the heart's electrical cycle that is determined by the heart rate, in a dose-dependant manner and can therefore increase the risk of arrhythmias. It is contraindicated in patients with pre-existing QT prolongation or together with QT prolonging drugs such as quinidine, sotalol, dofetilide, amiodarone, and erythromycin. It is mainly metabolized in the liver by CYP3A enzymes and, therefore, CYP3A inhibitors such as diltiazem, verapamil, ketoconazole, and grapefruit juice should not be co-administered with ranolazine since the risk of arrhythmias increases. Amlodipine does not inhibit CYP3A and can be used along with ranolazine. The dose of drugs such as simvastatin and digoxin should be decreased when ranolazine is simultaneously used. Ranolazine can increase blood pressure by as much as 15 mm Hg in patients with renal impairment. It is a pregnancy category C drug.

Aliskiren (Tekturna)

Aliskiren is the first of a new class of oral antihypertensives, the direct renin inhibitors.[3-4] It can be used as monotherapy or in combination with other antihypertensive agents. Aliskiren inhibits renin, thereby preventing conversion of angiotensinogen to angiotensin I, which is the first rate-limiting step in the renin-angiotensin-aldosterone system. This leads to decreased levels of angiotensin I, angiotensin II, and aldosterone and thus reduces arterial tone, renal sodium absorption, and aldosterone secretion—all resulting in decreased blood pressure. High-fat meals decrease absorption of aliskiren, and patients should establish a regular pattern of taking it either before or after meals. Dosage adjustment is not required in elderly patients or in those with mild to moderate renal or hepatic insufficiency.

The most common adverse effect is diarrhea, which is dose-related and occurs more in patients 65 years or older and in women. Cough occurs approximately a half to a third less often than with ACE inhibitors (ACEIs). Incidence of angioedema in studies is 0.06%. Other adverse effects are rash, elevated uric acid, gout, and renal stones. Hyperkalemia occurs less commonly when aliskiren is used as monotherapy. It is metabolized by cytochrome P450 3A4 and thus ketoconazole, which is a strong inhibitor of this enzyme, increases the aliskiren level by about 50%. Concurrent use of aliskiren with furosemide results in decreased serum concentration of furosemide, which could lead to a diminished effect of furosemide. No clinically relevant drug interactions occur when aliskiren is used along with atenolol, digoxin, amlodipine, hydrochlorothiazide, and ramipril. Several clinical trials have shown aliskiren to be an effective antihypertensive when used as monotherapy; it causes reduction in blood pressure similar to irbesartan. The combination of hydrochlorothiazide and aliskiren lowers blood pressure more than monotherapy with either drug alone. In pregnancy, it is a category C drug during the first trimester and category D during the second and third trimester.

At the present time, it doesn't appear that aliskiren will have any advantage over ACEIs or angiotensin receptor blockers (ARBs). It is very unlikely that addition of aliskiren to ACEIs or ARBs will offer additional antihypertensive effect and it may increase toxicity.

DIABETES MELLITUS

Sitagliptin (Januvia)

Sitagliptin is first in a new class of drugs called gliptins, which are inhibitors of the enzyme dipeptidyl-peptidase-4 (DPP-4). DPP-4 breaks down endogenous incretins, and gliptins such as sitagliptin inhibit this enzyme, increasing incretin hormone in the body. Incretin hormones increase insulin release in response to meals and decrease glucagon production in a glucose-dependent manner, lowering serum glucose concentrations. Sitagliptin has been approved for glucose control in patients with type 2 diabetes, and is to be used as monotherapy[5] or in combination with metformin or a glitazone (pioglitazone-Actos, rosiglitazone-Avandia). When taken orally, it is rapidly absorbed and excreted by the kidneys. Therefore the dose needs to be decreased in patients with moderate or severe renal disease. The most commonly reported adverse effects are symptoms of nasopharyngitis, upper respiratory infection, and headache. The incidence of hypoglycemia is no higher with sitagliptin than with placebo. Advantages of sitagliptin include lack of weight gain and low risk of hypoglycemia. Studies have shown that sitagliptin is less effective than sulfonylureas and metformin in lowering HbA1c.[6] It is a category B drug in pregnancy.

Exenatide (Byetta)

Exenatide is the first in a new class of antidiabetic drugs known as incretin mimetics.[7] It acts by stimulating glucagon-like peptide-1 (GLP-1) receptors, which causes stimulation of glucose-dependent insulin secretion, inhibits the release of glucagon after meals, and slows the rate of gastric emptying. It also suppresses appetite and

may aid in weight loss. It is a synthetic form of exendin found in the saliva of the Gila monster, which stimulates the pancreas. Exenatide is indicated as add-on therapy in patients with type 2 diabetes to improve glycemia when diabetes is not adequately controlled with oral hypoglycemic agents such as metformin and sulfonylureas.[8] It is not indicated as monotherapy. Exenatide is not a substitute for insulin in patients with type 1 diabetes. Its use in patients taking insulin, thiazolidinediones, meglitinides, or alpha-glucosidase inhibitors has not been studied.

It is administered subcutaneously in the thigh, abdomen, or upper arm. It should be taken twice daily, within 60 minutes of a morning and evening meal. The dose of sulfonylureas should be empirically decreased to reduce the risk of hypoglycemia, but this risk is less with metformin; hence the metformin dose does not have to be decreased. Other than hypoglycemia, adverse effects include nausea, vomiting, diarrhea, dizziness, headache, and dyspepsia, which are generally mild to moderate. Since exenatide is a protein molecule, antibodies may develop. However this does not affect the glycemic control significantly. Exenatide may affect the rate and extent of absorption of orally administered drugs as it slows gastric emptying.

Pre-filled pens are available, which can be kept at room temperature not to exceed 77° F for up to 30 days after the first use. The pen should be protected from light and should not be frozen. Exenatide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) or those with end-stage renal disease. It should not be used in patients with gastroparesis. It is a pregnancy category C drug.

MULTIPLE SCLEROSIS

Natalizumab (Tysabri)

Natalizumab is one of the new disease-modifying therapies for a relapsing form of multiple sclerosis.[9] It was temporarily removed from the market due to side effects but is once again available; however its use is restricted. It is a recombinant humanized monoclonal antibody produced in murine myeloma cells. Natalizumab acts by binding to the glycoprotein alpha 4beta1-integrin, which is an important mediator of cell adhesion and transendothelial migration. This blocks cell adhesion and interferes with the migration of autoimmune leukocytes across the blood-brain-barrier, which may interrupt the inflammatory changes in multiple sclerosis. It is administered by intravenous infusion over 1 hour once every 4 weeks.

The most frequently reported adverse effects are headache, fatigue, and arthralgias slightly higher than with the placebo. Severe adverse reactions include susceptibility to infections; hypersensitivity reactions include anaphylaxis and depression. Its use may also result in development of neutralizing antibodies to natalizumab, which is associated with loss of efficacy.[10] When interferon beta-1a is used along with natalizumab, the clearance of natalizumab is reduced by approximately 30%, which does not necessitate a dosage change. Results of any drug interactions with concurrent use of glatiramer are inconclusive. Studies have shown that use of natalizumab in multiple sclerosis results in a decrease in the number of relapses and new brain lesions. Its effect on disease progression is yet to be determined. It can be used as monotherapy or add-on therapy and should be considered for patients who cannot tolerate other therapies or have not benefited from other treatment options. It is a pregnancy category C drug.

HEPATITIS B INFECTION

Telbivudine (Tyzeka)

Telbivudine is the newest thymidine nucleoside analog approved by the FDA for the oral treatment of hepatitis B infection in patients 16 years or older.[11] It acts by blocking the hepatitis B virus (HBV) DNA polymerase, which is responsible for HBV infection in which there is evidence of active viral replication or persistent elevations in serum aminotransfersases—alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or histologically active hepatitis. Unlike lamivudine and adefovir, this drug has no known activity against human immunodeficiency virus (HIV) or other viruses. It is excreted by the kidneys; therefore the dose needs to be adjusted in patients with renal impairment. The most common adverse effects are fatigue, malaise, myopathy, diarrhea, gastritis, and headache. Patients should be cautioned not to discontinue treatment abruptly on their own because that may cause acute exacerbation of hepatitis B. Clinical studies have shown that telbivudine is more efficacious than lamivudine in HBeAg-positive patients and as effective as lamivudine in HBeAg-negative patients. Preliminary results from other trials have shown that telbivudine is also superior to adefovir. As is the case with other oral agents used in the treatment of hepatitis B infection, the role of telbivudine may be limited by the potential for hepatitis B viral resistance. Telbivudine is a pregnancy category B drug.

HYPONATREMIA

Conivaptan (Vaprisol)

Conivaptan is a vasopressin antagonist that has been

approved by the FDA for the short-term treatment of euvolemic hyponatremia in hospitalized patients.[12] Conivaptan acts by decreasing the permeability of vasopressin receptors in the renal collecting duct leading to excretion of free water. It is given intravenously after an initial bolus followed by a continuous infusion for up to 4 days if the response is inadequate in the first 24 hours. The most common adverse effects are infusion site reactions (50%), headache, thirst, hypokalemia, diarrhea, and orthostatic hypotension. Conivaptan inhibits CYP3A4 enzyme, therefore it is contraindicated with other CYP34 inhibitors such as itraconazole, clarithromycin, etc. It may cause rhabdomyolysis in patients taking statins. Overly rapid correction of serum sodium (ie, >12 meq/L/24 hours) may also occur and may result in neurologic complications due to osmotic demyelination. In patients with renal insufficiency, it can be used as an alternative to demeclocycline, which also inhibits the action of vasopressin but can cause nephrotoxicity. It is classified as category C drug for use during pregnancy.

PARKINSON'S DISEASE

Apomorphine (Apokyn)

Apomorphine is a dopamine agonist indicated for treatment of advanced Parkinson's disease during periods of "hypomobility," so-called "off-periods."[13] During these periods, the patients become immobile or unable to perform activities of daily living. In a clinical trial, patients with hypomobility treated with apomorphine showed significant (62%) improvement in Parkinson's disease rating scores compared to no improvement with a placebo. Apomorphine is given subcutaneously and is rapidly absorbed, with onset of action within 10-20 minutes that lasts about 60 minutes. Apomorphine can cause severe nausea and vomiting and has to be discontinued in 2%-3% patients. Hence, an antiemetic such as trimethobenzamide (Tigan) should be started 3 days before starting apomorphine and continued for at least the first 2 months of treatment. Apomorphine is contraindicated with other antiemetics, the 5HT3 antagonists such as ondansetron, because the combination can lead to severe hypotension and loss of consciousness. Also, dopamine antagonists like prochlorperazine (Compazine) or metoclopramide (Reglan) may antagonize effects of apomorphine and worsen Parkinson's symptoms. The most common adverse effects are yawning, dyskinesias, daytime sleep attacks, orthostatic hypotension, hallucinations, and peripheral edema. Hypersexuality and increased erections can also occur. Apomorphine is also associated with increase in QT interval and should be avoided in conjunction with other drugs that can prolong QT interval.

RHEUMATOID ARTHRITIS

Abatacept (Orencia)

Abatacept is the first in a new class of drugs approved for the treatment of rheumatoid arthritis. It selectively inhibits T-cell activation by blocking the interaction of CD80 and CD86 with CD28 required for T-cell activation.[14] This results in decreased serum concentrations of inflammatory markers, cytokines, and rheumatoid factor, which all play an important role in the pathogenesis of rheumatoid arthritis. Abatacept should be used in patients with moderate to severe rheumatoid arthritis who have not responded to tumor-necrosis factor (TNF) inhibitors[15] such as etanercept (Enbrel) or 1 or more disease-modifying anti-rheumatic drugs (DMARDs) such as anakinra (Kineret). It can be used as monotherapy or in combination with a DMARD but not with TNF-inhibitors or anakinra. It is given intravenously over 30 minutes. The most common adverse effects are headache, symptoms of nasopharyngitis, and nausea, but the most serious effects are infections and increased risk of malignancies. Patients should be tested for tuberculosis before starting treatment with abatacept and should not be given live vaccines while on treatment or afterward for 3 months. Patients treated concurrently with abatacept and TNF-inhibitors are at an increased risk for serious infections with no improved efficacy. Patients with COPD, treated with abatacept, may develop more adverse respiratory effects than with placebo. It is a pregnancy category C drug.

PAIN

Pregabalin (Lyrica)

Pregabalin is the newest agent approved by the FDA for the treatment of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy and for adjunctive treatment of partial onset seizures in epileptic patients. It is an analogue of gamma-aminobutyric acid (GABA) that binds selectively to the alpha2-delta subunit of the calcium channels resulting in a decrease of calcium influx at nerve terminal. This reduces the release of various neurotransmitters, including glutamate, norepinephrine, and substance P, which in turn results in its analgesic, anti-convulsant, and anxiolytic effects.[16]

The most common adverse effects include dizziness and somnolence. Other side effects include fatigue, dry mouth, peripheral edema, headache, and difficulty with

concentration/attention. It is excreted almost entirely unchanged in the urine. It does not interact with other anticonvulsants. Clinical studies in patients with postherpetic neuralgia and diabetic peripheral neuropathy have shown that pregabalin treatment resulted in a significant decrease in mean pain score at the endpoint, compared to a placebo. Pregabalin is structurally similar to gabapentin but is more potent than gabapentin and achieves efficacy at lower doses, which may result in less fatigue and other side effects.[17] It may be indicated in patients who cannot tolerate other medication for neuropathic pain. The Drug Enforcement Administration (DEA) has classified pregabalin as a schedule V drug due to its potential for physical dependence.

CONSTIPATION

Lubiprostone (Amitiza)

Lubiprostone is the first selective chloride channel activator approved for the treatment of chronic idiopathic constipation in all adults. It is an alternative for patients over 65 years for whom tegaserod is not indicated/approved. It activates CIC-2 chloride channels in the gastrointestinal tract leading to increased intestinal secretion and motility and improved stool consistency.[18-19] Lubiprostone should be used in patients with constipation who have not responded to use of fiber or laxatives. The common adverse effects include headache, nausea, and diarrhea. Nausea decreases with once daily dosing and when taken with food. Clinical trials have shown that lubiprostone increases bowel movements by approximately 3 per week. Study results were similar regardless of gender, age, or race. Studies have also reported continued efficacy in decreasing constipation severity, abdominal bloating, and discomfort for up to 1 year. Lubiprostone is a category C drug in pregnancy.

INSOMNIA

Ramelteon (Rozerem)

Ramelteon is the first highly selective melatonin type 1 (MT1) and type 2 (MT2) receptor agonist approved for the treatment of insomnia in adults characterized by difficulty with sleep onset.[20] It is unlike other prescription hypnotics and is not a controlled substance. Ramelteon has no measurable affinity for the GABA receptor complex or for benzodiazepine, dopamine, or opiate receptors. There is no drug abuse potential or "hangover" effects like those often associated with other agents used to treat insomnia. Also, unlike zolpidem extended release (Ambien CR) and eszopiclone (Lunesta), ramelteon can be used long-term and is well tolerated in elderly patients. Its onset of action is approximately 30 minutes and patients should take it within 30 minutes of going to bed. The most commonly reported side effects are headache, dizziness, and somnolence. In 1 study, ramelteon increased serum prolactin level. Ramelteon undergoes extensive first-pass metabolism and is predominantly metabolized by the hepatic cytochrome P 450 isoenzyme 1A2. Fluvoxamine (Luvox) an SSRI, is a strong inhibitor of this enzyme and has been shown to markedly increase serum concentration of ramelteon, so the 2 drugs should not be used simultaneously. Ciprofloxacin is also a CYP1A2 inhibitor and may have similar effect. Rifampin, which induces CYP enzymes, significantly decreases serum levels of ramelteon when used with it concurrently. Clinical trials using polysomnography have shown that ramelteon decreases mean latency to persistent sleep by 7.5 to 15.7 minutes and increased total sleep time by 11.6 to 19 minutes compared to placebo.[21] Ramelteon is a pregnancy category C drug.

SMOKING

Varenicline (Chantix)

Varenicline is the first partial nicotine agonist approved for smoking cessation in individuals older than 18 years of age.[22] It is an alpha-4-beta-2 nicotine acetylcholine receptor partial agonist and has greater affinity than nicotine but stimulates receptor-mediated activity at a significantly lower level than nicotine. This partial nicotine effect blocks the pleasurable effects of smoking and also decreases the withdrawal symptoms from nicotine. Varenicline is absorbed from gastric mucosa and is minimally metabolized and excreted unchanged by the kidneys, therefore the dose needs to be adjusted in patients with severe renal impairment (estimated creatinine clearance of <30 ml/min). The most common adverse effects are nausea, sleep disturbance, headaches, abnormal dreams, constipation, flatulence, and xerostomia. Nausea decreases when it is taken after eating and with a full glass of water.

Clinical studies have shown varenicline to be effective in reducing the urge to smoke and more patients maintained abstinence than with a placebo. Patients treated with varencline also reported significantly greater decrease in craving and withdrawal symptoms compared to placebo-treated patients. It is also more effective than bupropion (Zyban) in increasing smoking cessation rates, but does not reduce the weight gain after smoking cessation that occurs in patients using bupropion. Patients should be advised to set a "target quit date" and varenicline should be started 1 week before that date and continued for 12 weeks. For patients who have success-

Appendix. Summary of The Drugs Discussed

Drug	Indication	Pregnancy Adverse Effects	Category	Route/Comments
Ranolazine (Ranexa)	Chronic stable angina	Dizziness, headache, constipation, can increase QT interval	C	Taken orally Does not decrease blood pressure and heart rate
Aliskiren (Tekturna)	Hypertension	Diarrhea, cough, gout	First trimester C Second and third trimester D	Taken orally
Sitagliptin (Januvia)	Type 2 diabetes mellitus	Nasopharyngitis, hypoglycemia, headache	B	Taken orally Advantage-lack of weight gain
Exenatide (Byetta)	Add-on therapy in treatment of Type 2 diabetes mellitus	Hypoglycemia, nausea, vomiting, dyspepsia, headache	C	Subcutaneous May aid in weight loss
Natalizumab (Tysabri)	Relapsing form of multiple sclerosis	Headache, fatigue, arthralgias	C	IV Infusion
Telbivudine (Tyzeka)	Hepatitis B infection	Fatigue, malaise, myopathy, gastritis	B	Taken orally
Conivaptan (Vaprisol)	Euvolumic Hyponatremia	Infusion site reactions, orthostatic hypotension, hypokalemia	C	Intravenous Alternate to Demeclocycline in patients with renal insufficiency with hyponatremia
Apomorphine (Apokyn)	Parkinsons' disease during periods of "hypomobility"	Dyskinesias, peripheral edema, nausea, vomiting		Subcutaneous Hypersexuality Can increase QT interval
Abatacept (Orencia)	Rheumatoid arthritis—moderate to severe	Nasopharyngitis, nausea, headache	C	Intravenous Increased risk of infections and malignancies
Pregabalin (Lyrica)	Neuropathic pain in post-herpetic neuralgia and diabetic peripheral neuropathy	Dizziness, somnolence		Taken orally Scheduled V drug (potential for physical dependence)
Lubiprostone (Amitiza)	Chronic constipation	Headache, nausea, diarrhea	C	Taken orally
1Ramelteon (Rozerem)	Insomnia	Headache, dizziness, somnolence	C	Taken orally No abuse potential Can be used long-term Well tolerated in elderly
Varenicline (Chantix)	Smoking cessation	Sleep disturbance, abnormal dreams, xerostomia	C	Taken orally
Human Papilloma Virus (Types 6, 11, 16, 18) Vaccine (Gardasil)	Prevention of diseases caused by Human Papilloma Virus (Types 6, 11, 16, 18)	Injection site reactions	B	Intramuscular Not indicated in the treatment of active genital warts, cervical carcinoma, etc
Herpes Zoster Vaccine (Zostavax)	Prevention of Herpes Zoster	Injection site reactions		Subcutaneous Contraindicated in immuno-compromised patients and those on immunosuppressive therapy or those with active untreated tuberculosis

fully stopped smoking during the first 12 weeks, an additional course of 12 weeks is recommended to further increase the likelihood of long-term abstinence.[23] The safety and efficacy of co-administration of varenicline with other smoking cessation aids has not been established. Varenicline is a pregnancy category C drug.

VACCINES

Human Papilloma Virus (Types 6, 11, 16, and 18) Recombinant Vaccine (Gardasil)

Gardasil is the first vaccine approved for the prevention of human papilloma virus (HPV) types 6, 11, 16, and 18.[24] Approximately 95% of anogenital warts are caused by HPV types 6 and 11 and more than 70% of cervical cancers and high-grade cervical intraepithelial neoplasia (CIN) are caused by HPV types 16 and 18. It has no effect against non-vaccine HPV types, and infected women may develop sequala associated with non-vaccine HPV types. Hence, Gardasil does not eliminate the need for routine cervical screening. Gardasil acts by stimulation of antibody production in vivo against the above 4 types of HPV. It is indicated for females 9-26 years old. It is given as 0.5 ml intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh at 0, 2, and 6 months.

The most common adverse effects are injection site reactions including pain, swelling, erythema and pruritis, and fever. It can be given at the same time with a hepatitis B vaccine but at a different site. Patients should not be on immunosuppressive treatments such as antimetabolites, alkylating agents, cytotoxic agents, and corticosteroids or with impaired immune response such as in human immunodeficiency virus (HIV) infected patients since these can decrease the immune response to the vaccine. The vaccine is not indicated in the treatment of active genital warts, cervical cancer, or CIN. It is contraindicated in patients with bleeding disorders like hemophilia or thrombocytopenia or on anticoagulants because of the increased risk of bleeding and hematoma formation. In pregnancy, it is rated as a category B risk.

Herpes Zoster Vaccine (Zostavax)

Herpes zoster vaccine is a live attenuated vaccine approved for prevention of herpes zoster (shingles) in patients 60 years or older. This vaccine protects against the development of zoster by boosting cell-mediated immunity.[25] It is not indicated to treat herpes zoster or post-herpetic neuralgia. It is administered subcutaneously, as a single dose. The most common adverse effects are injection site reactions such as erythema, pain, swelling, and pruritus. These are generally mild. This vaccine is contraindicated in persons who are immunocompromised, such as those with primary or acquired immunodeficiency including leukemia, lymphoma, or AIDS, or those receiving immunosuppressive therapy including high doses of corticosteroids (prednisone >20 mg/day), or cytotoxic chemotherapy. It is also not indicated in patients with a history of an anaphylactic reaction to gelatin, neomycin, or other components of the vaccine. Herpes zoster vaccine should not be given to patients with active, untreated tuberculosis.

Varicella (chickenpox) vaccine (Varivax) used in children to vaccinate against varicella and herpes zoster vaccine (Zostavax) to prevent herpes zoster in adults are not interchangeable as herpes zoster vaccine is 14 times more potent than varicella vaccine because higher potency is needed to elicit cell-medicated immunity in adults. A clinical study has demonstrated that herpes zoster vaccine decreases the risk of herpes zoster infection by half, reduces the severity and duration or pain and discomfort by 61%, and prevents post-herpetic neuralgia by 67%.

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WISCONSIN MEDICAL JOURNAL

Updated CDC Guidelines for HIV Testing: A Review for Wisconsin Practitioners

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ABSTRACT

An estimated 250,000 people in the United States are living with undiagnosed human immunodeficiency virus (HIV) infection. Those who are unaware they are HIV-infected miss opportunities for early treatment and may unknowingly infect others. Early identification of HIV-infected individuals benefits both the infected individuals and the health of the public. To decrease the number of individuals unaware that they are HIV-infected, the Centers for Disease Control and Prevention (CDC) recently revised its recommendations for HIV testing in health care settings. Changes in the CDC-recommended HIV testing protocol include expanding the population to be routinely tested and streamlining the testing and consent process. This article discusses the CDC recommendations, current Wisconsin laws regarding HIV testing, challenges associated with reconciling these laws with current CDC guidelines, and ethical concerns surrounding the guidelines. The authors conclude that Wisconsin health care professionals should adopt the CDC recommendations for HIV testing. However, to fully implement the revised CDC testing protocol, Wisconsin law will need to be amended. Adoption of these recommendations would increase the number of people in Wisconsin who are aware of their HIV-positive status and can then receive timely treatment and information about preventing HIV transmission.

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INTRODUCTION

In the past decade, significant advances have been made in the treatment of individuals with human immunodeficiency virus (HIV) infection. When successfully implemented, today's HIV care practices can slow the clinical progression of the disease, improve the quality of life of persons living with HIV, and reduce HIV-related mortality. Under the traditional model of risk-based HIV testing (testing only those patients who report practicing HIV risk behaviors), many HIV-infected individuals are not diagnosed with HIV until they have advanced HIV infection or acquired immune deficiency syndrome (AIDS).[1-3] For example, 45% of all patients diagnosed with AIDS between 2000 and 2003 were first diagnosed with HIV less than 1 year prior to being diagnosed with AIDS, an advanced stage of immunosuppression during which opportunistic infections often occur.[3] Thus, for many HIV-infected persons, access to clinical HIV care and timely information on preventing HIV transmission are significantly delayed because they are unaware of their HIV status.

At present, approximately 250,000 people in the United States are living with an undiagnosed HIV infection.[4] These individuals are at risk for complications of untreated HIV, and of unknowingly transmitting the virus to others. The Centers for Disease Control and Prevention (CDC) estimates that more than half of the approximately 32,000 new sexually-transmitted HIV infections that occur each year result from the sexual activities of persons with HIV who are unaware of their serostatus.[5] Many HIV-positive persons, once aware of their HIV infection, decrease high-risk sexual behaviors with HIV-negative partners.[6-7] Thus, diagnosing prevalent HIV infections is an essential tool for reducing new transmissions.

The availability of reliable, inexpensive, and noninvasive HIV antibody tests and effective HIV therapy has led many public health leaders to advocate for

the expansion of routine, voluntary HIV screening.[8-9] Screening involves performing a test for HIV antibodies on either blood or oral fluid in asymptomatic patients. Rapid tests are available that can provide results in about 20 minutes in appropriate settings. Those patients who are positive must undergo confirmatory testing with a Western Blot test.

In 2006, the CDC issued revised HIV testing recommendations to encourage the adoption of universal screening for patients age 13-64 years, without regard to risk behavior, and in all medical settings. These guidelines recommend changes regarding who should be tested for HIV, the consent process for HIV testing, and whether HIV prevention counseling should accompany all HIV testing.

Here we provide a synopsis of the CDC's recommendations and the rationale underlying the specific protocol advanced by the CDC. We then discuss current Wisconsin law regarding HIV testing, challenges associated with reconciling state law with current CDC guidelines, and ethical concerns surrounding the guidelines.

THE CDC RECOMMENDATIONS

The essential elements of the 2006 CDC *Revised Recommendations for HIV Testing* are:

1. All patients ages 13-64 years should be screened for HIV, in all medical settings, without regard to risk.
2. Separate written consent for HIV testing should not be required.
3. HIV prevention counseling should not be a prerequisite for HIV testing.[10]

All 3 elements represent significant changes from prior CDC recommendations. In prior guidelines, routine testing was recommended only in specific circumstances, and written consent and prevention counseling for each tested person was recommended as a standard practice.[11] Table 1 presents an overall summary of key differences and similarities between the 2006 recommendations and previous CDC guidelines. Details regarding the changes are provided below.

Who Should Be Tested

The 2006 guidelines recommend that health care professionals perform routine HIV screening for all patients ages 13-64, without regard to a patient's stated history of HIV transmission risk. All patients should be tested at least once and patients who may be at high risk for HIV should be tested annually. Those considered at high risk for HIV include injection-drug users and their sex partners, people who exchange sex for money or drugs, sex partners of HIV-infected persons, and people who have had more than 1 sex partner since their most recent HIV test or whose sex partners have had more than 1 sex partner since their most recent HIV test.

These recommendations apply to all health care settings, including emergency departments, urgent care clinics, inpatient services, and primary care settings. Institutions or practices that can demonstrate that the prevalence of undiagnosed HIV infection in their patient population is <0.1% are exempt from the recommendations. In settings without such data, professionals are encouraged to begin screening and continue until such time as their testing experience shows that <1 in 1000 of their patients are HIV-positive.

Previously, the CDC had recommended that hospitals with high AIDS diagnosis rates (>1 per 1000 patient discharges) institute routine, universal screening of all patients age 14-54.[11] Institutions with lower AIDS diagnosis rates were advised to test patients based on their reported HIV risk behaviors.

Consent for Testing

In their previous (2001) HIV testing guidelines, the CDC recommended that consent for an HIV test be procured after a discussion with the patient about HIV testing.[12] Further, once the patient consented to be tested, professionals were advised to document that consent with the patient's signature on a form specifically designated for HIV testing consent.

The 2006 CDC guidelines streamline this process. After providing brief information about HIV testing (including information on HIV infection and the meaning of positive and negative test results), physicians are advised to inform patients that a routine HIV test will be administered unless the patient chooses to decline such testing. If the patient does not actively decline testing, it can be performed. (This "opt-out" approach is discussed further below.) Furthermore, the CDC no longer advises that physicians document a patient's consent for HIV testing with a signature on a specific HIV testing consent form. Instead, the patient's general consent for medical care, coupled with his or her lack of dissent when informed that a routine HIV test will be conducted, implies consent for HIV testing.

It should be noted that the elimination of signed documentation of consent is in conflict with current Wisconsin law, which requires a designated consent form for HIV testing. This and other legal aspects of HIV testing consent and its documentation are discussed in more detail later in this article

HIV Prevention Counseling

The revised CDC recommendations further streamline

Table 1. Essential Elements of 2001 and 2006 CDC HIV Testing Guidelines

	2001 Guidelines	2006 Guidelines
Population to be tested	• All high-risk patients • All patients in high-prevalence settings (>1%) • In other settings: based on individual risk	• All patients ages 13 to 64, without regard to risk • High-risk patients, annually[a]
Pretest information	• An explanation of HIV and the meanings of positive and negative test results should be discussed Patient questions should be answered	• Same as previous guidelines
Consent	• Written consent should be documented on HIV-specific consent form	• Consent is inferred by general medical consent, once HIV testing is discussed and the patient did not dissent[b]
HIV prevention counseling	• Should accompany HIV testing	• Not required, but encouraged for high-risk patients and in high-risk settings (eg, STD clinics)

[a] Patients at high risk for HIV include: injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and persons who themselves or whose sex partners have had more than 1 sex partner since their most recent HIV test.
[b] This CDC recommendation conflicts with current Wisconsin law.

the testing process by eliminating the requirement of HIV prevention counseling in conjunction with ordering HIV tests. HIV prevention counseling is an interactive process that consists of: (1) assessing an individual's risk for acquiring or transmitting HIV based on a discussion of his or her risk behaviors, and (2) developing an individualized plan to reduce these risk behaviors.[12] Although health care professionals have the discretion to discuss HIV risk behaviors with patients, prevention counseling is no longer considered a prerequisite for HIV testing. However, prevention counseling is still encouraged for patients known to be at high risk for acquiring HIV. Moreover, the guidelines continue to recommend that pretest information be provided to patients, including an explanation of HIV infection and the meanings of positive and negative test results. Patients also should have an opportunity to ask questions about testing prior to being given the option to decline it.

RATIONALE FOR REVISED TESTING PROCEDURES

Routine Screening

Routine screening refers to testing all patients in a particular setting without regard to the risk of any individual patient. When applied in other settings, namely with blood donors and pregnant women, routine HIV screening programs have been quite successful.[11,12] Universal screening of all blood donors in the United States, first with antibody tests and more recently with more sensitive nucleic acid tests, has essentially eliminated transfusion-related HIV transmission.[14] Routine screening of pregnant women has allowed health care professionals to take appropriate prophylactic measures to prevent HIV transmission to infants, such as administering perinatal antiretroviral therapy to HIV-positive women and prophylactic antiretrovirals to newborns. Universal prenatal screening and the subsequent prevention efforts that follow have dramatically decreased cases of perinatal HIV-transmission in the United States, from a peak of 1650 cases in 1991 to an estimated 144-236 cases in 2002.[15-17] The CDC cites these successes as a primary rationale for expanding routine screening to the general population.

Opt-out Testing and Elimination of Written Consent

The CDC recommends that health care professionals adopt an "opt-out" approach to HIV screening. In "opt-out" screening, patients are informed that they will be tested for HIV unless they specifically decline testing. This approach contrasts with "opt-in" testing in which patients must actively agree to testing by giving their assent. Both "opt-in" and "opt-out" testing can be coupled with a policy of routine testing (testing all patients without regard to risk) or with risk-based testing.

Routine HIV testing implemented through an "opt-

out" approach may reduce patients' anxiety about HIV testing, and may in turn result in higher rates of testing. Pregnant women offered HIV tests in an "opt-out" program reported feeling less embarrassed because they did not have to affirmatively request or consent to testing.[18] In addition, a higher proportion of women had HIV tests performed when "opt-out" testing was instituted.

The elimination of separate consent for HIV may further increase the number of HIV tests performed. The San Francisco Department of Public Health Medical Care System observed a significant increase in the rate of HIV testing after that system abandoned requirements for designated written consent and separate laboratory requisitions for HIV tests.[19] The CDC cites these findings to support the changes in the current recommendations, reasoning that these changes will make HIV testing more acceptable and more routine to patients, ultimately resulting in more individuals being tested.

Elimination of Prevention Counseling Requirements

Simplification of the HIV testing process in health care settings includes removing the requirement that prevention counseling accompany testing. This change is based on the questionable efficacy of prevention counseling performed in health care settings. Individually tailored behavioral prevention messages, especially when delivered to HIV-positive persons, have been shown to be effective in reducing sexual risk behaviors.[7,20] However, physician-delivered prevention counseling to HIV-negative patients in health care settings has not been proven effective.[20] (Currently, such counseling is only provided with approximately 35% of all HIV tests performed by health care professionals.[21]) In addition, elimination of the counseling requirement should decrease the time needed for the testing process, which could increase professionals' willingness to offer the test to their patients.

Cost-effectiveness

The CDC also considered the cost-effectiveness of implementing universal HIV screening for persons ages 13-64. HIV testing using a rapid HIV antibody assay costs approximately $33 per HIV-negative patient, with higher costs for patients who test HIV-positive.[22] Based on published cost-effectiveness studies of HIV testing, the CDC concluded that HIV screening in populations with a prevalence of undetected infection of 0.1% or more is as cost-effective as screening for other diseases such as hypertension and colon cancer.[23-24] When the prevalence of undetected infection equals 1%, the cost-effectiveness ratios for HIV screening range from $15,078 to $38,000 per quality-adjusted life-year saved.

To determine whether expanded HIV screening would have a similar cost-effectiveness ratio in Wisconsin, the state's HIV prevalence needs to be considered. The prevalence of diagnosed HIV infection in Wisconsin varies widely.[25] The lowest prevalence is found in the northern, northeastern, and western counties, with an HIV prevalence of approximately 0.04% to 0.05%. Southern Wisconsin is estimated to have a prevalence of 0.11% and southeastern Wisconsin has a prevalence of 0.18%. The highest prevalence in the state is found in the north-central part of the city of Milwaukee among persons age 25-34, where the prevalence is estimated to be 1.6%.[26]

The prevalence of undiagnosed infection is expected to be approximately a third as large as the prevalence of diagnosed infection.[4] Conversely, throughout Wisconsin, it is likely that the actual prevalence of HIV in the age group targeted by the CDC guidelines (ages 13-64) is greater than the estimates given above. Those rates are for the general population, which includes children and the elderly, groups that are known to have a lower rate of HIV infection than the target population.

In summary, it is unclear whether implementing the CDC recommendations for testing in every area of Wisconsin would be cost-effective. However, the cost-effectiveness of routine HIV screening in southern and southeastern Wisconsin is likely to be acceptable. Moreover, elimination of the requirement for prevention counseling should decrease costs and thereby improve the cost-effectiveness of HIV screening.[27]

WISCONSIN'S HIV TESTING LAW

Under current Wisconsin law, patients or their health care agents must provide written, informed consent prior to being tested for HIV.[28] The law requires documentation of patient consent on a form designed specifically for consent to HIV testing. The consent form must include the patient's name, the consenting person's signature, and the date of the signing. The consent form also must describe circumstances under which disclosure of HIV test results may be permissible, such as when a health care worker is significantly exposed to the patient's blood or body fluids[29] or when a victim of specified sexual crimes is significantly exposed to the perpetrator's blood or sexual body fluids.[30] If health care professionals prefer, the consent form can specify that materials outlining permissible HIV test result disclosures are available on request. Individuals 14 years of age and older can consent to be tested without parental consent.[31] Consent from a legally authorized adult

is normally required prior to testing children under 14 years of age.

Wisconsin law also requires health care professionals to provide patients with information on HIV and pertinent resources during the HIV testing process. According to the statute, any provider or agency that tests people for HIV must "provide counseling about HIV and referral for appropriate health care and support services as necessary."[32] The HIV counseling and referral requirement does not describe how or when such information is to be provided or the circumstances under which counseling and referrals are deemed "necessary."

For the most part, Wisconsin law related to HIV testing could support the new CDC testing guidelines. In Wisconsin, health care professionals have the discretion to offer HIV tests to all of their patients as long as the patients are informed that they will be tested and provide consent. Thus Wisconsin law is consistent with the CDC guidelines, which require health care professionals to inform patients that an HIV test will be conducted and that they have the right to decline. Wisconsin law also requires persons administering HIV tests to offer information and referrals to patients when appropriate. Although the nature of the information and when it is to be shared is left unspecified, the Wisconsin Department of Health and Family Services has adopted the CDC position that prevention counseling should not be a barrier to HIV testing (written communication, Michelle Llanas, Wisconsin Division of Public Health, March 2007). In short, if prevention counseling is not practicable, health care professionals are encouraged to forgo counseling and administer the HIV test rather than not testing the patient at all. This position is consistent with the CDC's new policy.

The explicit provisions in the Wisconsin legal code that require documentation of informed consent for HIV testing are in conflict with the CDC guidelines. Wisconsin law requires patients to sign a specific form to document that they are aware of permissible disclosures of HIV test results and that they consent to be tested. In contrast, the CDC guidelines suggest that a patient's general consent for health care serve as consent to be tested for HIV. To bring Wisconsin law in line with the CDC recommendations, provisions requiring professionals to document consent to HIV testing differently than they document general consent for diagnosis and treatment would need to be eliminated. For the sake of clarity, the statute could also be amended to specify that prevention counseling is not required in general medical settings.

ETHICAL CONCERNS

Some physicians may be troubled about the new "opt-out" consent process and the elimination of the specifically designated consent form.[33] Historically, there has been considerable resistance to universal HIV screening programs in the United States.[34] The most common concerns are that the rights of people identified as HIV-positive will be compromised or violated and that HIV-positive persons will be subject to abuse and discrimination.[35] The history of HIV-related stigma and discrimination in the United States supports these concerns. HIV-positive persons have been evicted from housing, banned from schools, rejected by health care professionals, and terminated from jobs, largely because of the misperception that they pose a threat to the health and welfare of others.[36-37] At various times during the US epidemic, HIV-positive persons' rights, including the right to privacy, have been severely compromised.[36]

One of the premises on which the newest CDC HIV testing recommendations are built is that the US social climate for persons living with HIV is more positive than it was in the early years of the US epidemic. In the last 20 years, a variety of laws have been enacted to protect HIV-positive persons against discrimination.[38] In Wisconsin, for example, there are penalties for health care professionals who breach state HIV testing laws or discriminate against persons living with HIV. These penalties are designed to deter or to punish inappropriate disclosure of HIV test results to others[39] or to prohibit HIV-related discrimination by persons to whom an individual's positive serostatus has been disclosed.[40] Instances of the most overt forms of HIV-related discrimination in Wisconsin and elsewhere have become relatively rare.

Still, mechanisms to protect the confidentiality of information related to HIV status and to deter and punish HIV-related discrimination remain important. Although the CDC guidelines advocate a streamlined HIV testing process, nothing in the guidelines suggests limiting existing protections against inappropriate disclosure of HIV test results or HIV-related discrimination. With expanded testing, these protections become even more critical. If changes in Wisconsin law are made to support the full adoption of the CDC's new testing guidelines, an assessment of the adequacy of Wisconsin laws to protect HIV-positive persons against discrimi-

nation and breaches of confidentiality should be conducted as well.

DISCUSSION

Wisconsin practitioners should consider adopting the revised CDC guidelines to make HIV testing a routine part of patient care. Routine screening could reduce the risk of HIV-transmission to uninfected individuals and improve the health of those living with HIV disease. If HIV-infected individuals are diagnosed earlier during the course of infection, they will have a greater opportunity to benefit from antiretroviral therapy, which can preserve immune system function, prevent opportunistic infections, and increase quality and length of life. In addition, these individuals will then have the opportunity to receive appropriate prevention education and to make informed behavioral choices, which could decrease new HIV transmissions.

Wisconsin law will support the implementation of the revised recommendations, for the most part. However, Wisconsin law continues to require health care professionals to obtain written consent for HIV testing on a separate consent form. Therefore, full adoption of the CDC recommendations, including the streamlined consent process, will require changes to existing Wisconsin law. Amendments to state law to allow full implementation of the CDC guidelines are being considered (written communication, Joseph P. Hoey, Office of Wisconsin State Representative Sheldon Wasserman, June 5, 2007), but until the law is amended, health care professionals must continue to obtain written informed consent for testing on an HIV testing consent form. If the requirement of written consent specific to HIV testing is eliminated, a review of the legal protections regarding patient confidentiality and disclosure of HIV diagnoses should be conducted.

Even in the absence of a legal requirement for separate written consent, it remains the responsibility of health care professionals to properly inform patients about HIV testing, to answer patients' questions regarding testing, to allow for dissent prior to testing, and to maintain the confidentiality of test results. As health care professionals, it is our duty to balance efficient and comprehensive diagnosis and treatment, health promotion and disease screening, and the autonomy and individual rights of our patients.

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WISCONSIN MEDICAL JOURNAL

Practical Approach to Metabolic Evaluation and Treatment of the Recurrent Stone Patient

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ABSTRACT

Although significant progress has been made during the last 3 decades in the minimally invasive surgical management of stone disease, the medical prevention of urolithiasis still remains challenging as much less progress has been achieved during the same time period. The purpose of this article is to provide the practicing urologist with practical guidelines for the metabolic evaluation and management of the recurrent stone patient. The recommendations are based on the latest available information regarding the pathogenesis, medical treatment options, and decision-making rationale when managing these challenging patients.

INTRODUCTION

Kidney stones affect approximately 15% of men and 7% of women in the United States, at an estimated cost of more than $2 billion per year.[1] Recent epidemiologic data suggest an increasing prevalence and incidence of kidney stones.[2] Modern lifestyle, obesity, and changing dietary habits are some of the factors that have been attributed to this increase in incidence.

The last 3 decades have seen significant advances in the surgical management of stone disease. Minimally invasive techniques including ureteroscopy, extracorporeal shock wave lithotripsy (SWL), and percutaneous nephrostolithotomy (PNL) have essentially replaced open stone surgery for the management of stone disease today. This has resulted, in part, in tempered interest in medical management for urinary calculi. Although most of these procedures are performed on an outpatient basis or during a short hospital stay, they have the potential for morbidity and long-term side effects. Additionally, repeat surgical treatment of recurrent stones in these patients is associated with increased financial burden. The prevention of stone formation by medical therapy has been shown to be cost-effective and is thus a logical extension of care.[3]

This article addresses patients who are at high risk of recurrent stone formation and provides guidelines for medical management.

EVALUATION OF A FIRST-TIME STONE FORMER

First-time stone formers have been estimated to have a 50% risk of recurrence within the subsequent 10 years. In a northern European population, a prospective evaluation noted an overall rate of recurrence of 53% within 8 years.[4]

The decision to investigate a first-time stone former remains controversial. Even though up to 50% of patients with a stone will have recurrence, more than 50% of all recurrent calcium stone formers have only 1 recurrence during their lives and only 10% of recurrent stone formers have more than 3 recurrences.[5] Although the remission rate of medical prophylaxis in calcium stone formers is 80%, recent data suggest that medical prevention in patients who form stones less frequently than once every 3 years may not be cost-effective.[6]

However, formation of a kidney stone may be the harbinger of a more severe underlying systemic disorder like renal tubular acidosis or hyperparathyroidism. All first-time stone formers should at least have a simplified evaluation (Table 1) to rule out any severe underlying systemic disorders that may cause recurrent calculi and extrarenal complications. A careful medical history is an important part of the evaluation as it may disclose any underlying dietary habits, medical conditions, and medications that contributed to the stone

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Table 1. Simplified Evaluation of Low-risk First-time Stone Formers

History
Predisposing medical conditions (as in Table 2)
Medications
Dietary history (fluid, calcium, oxalate, and purine intake)
Family history of stone disease
Occupational history (excessive fluid loss)
Blood Screen
Basic metabolic panel
Calcium
Parathyroid hormone
Uric acid
Urine
Urinalysis
Urine culture
Radiography
KUB (Kidney, ureter, and bladder)
Computed tomography (CT) scan or intravenous pyelography
Stone analysis

disease. A multichannel blood screen, including measurement of serum calcium, uric acid, and parathyroid hormone, should be obtained.

Proper identification of stone composition is fundamental in the risk evaluation. This is best done with either roentgen crystallography or infrared spectroscopy; it is recommended that all patients have at least 1 stone analyzed. Patients with uric acid, cystine, and infection stones have a high incidence of recurrent stone formation. The presence of uric acid or cystine suggests gouty diathesis or cystinuria, respectively. The finding of struvite, carbonate apatite, and magnesium ammonium phosphate suggests lithiasis of infection origin. Calcium stones are less useful diagnostically as they may occur in several conditions, including hypercalciuria, hyperuricosuria, enteric hyperoxaluria, hypocitraturia, and low urine volume.[7] However, it may be important to know if the calcium stone was mixed. A predominance of a hydroxyapatite component suggests renal tubular acidosis or primary hyperparathyroidism. There is also evidence to suggest that calcium oxalate stones with significant calcium phosphate or calcium oxalate dihydrate content have a higher recurrence rate than pure calcium oxalate monohydrate stones.[8]

An indirect approach for analysis using radiologic information and urinalysis can be applied. Radiologic evaluation can also rule out any anatomic abnormality associated with recurrent stone formation. Uric acid stones are radiolucent on KUB (kidney, ureter, and bladder) and radiopaque on computed tomography (CT) scan. Other stones such as ammonium urate, sodium urate, xanthine, and 2,8-hydroxyadenine have similar properties. Further clues in support of the uric acid diagnosis are a high serum level of urate, low urine pH, and the appearance of uric acid crystals in the urine. Struvite and cystine stones have a much lower radiographic density than calcium stones. Struvite stones are usually accompanied by a history of infection with urease producing bacteria and have a staghorn and multilayered morphology. The microscopic demonstration of coffin-like crystals is diagnostic for struvite. Cystine stones are associated with a positive nitroprusside test and flat hexagonal crystals on a urinalysis.

EVALUATION OF A HIGH-RISK OR RECURRENT STONE FORMER

A more extensive evaluation is warranted in individuals with recurrent nephrolithiasis as well as in patients at an increased risk for further stone formation (Table 2). This extensive evaluation was first described by Pak et al in 1980 and later modified by Levy et al in 1995.[9,10] The evaluation is completed in 2 outpatient visits (Table 3). It is preferable that patients discontinue any medication that may interfere with calcium, uric acid, or oxalate metabolism both before and during the evaluation. These include vitamins C and D, calcium supplements, antacids, diuretics, and acetazolamide.

The first visit includes all the testing done in the simplified evaluation as mentioned above, along with 2 24-hour urine specimens on a random diet. On the second visit, the patient brings in a third sample of 24-hour urine on a restricted diet (400 mg calcium and 100 mEq sodium/day). This dietary restriction is imposed to standardize the diagnostic tests, to better assess the cause of hypercalciuria, and to prepare for the "fast and calcium load" test. This test is performed on the morning of the second visit to identify the cause of hypercalciuria (absorptive versus resorptive versus renal leak). After overnight hydration with 600 ml of water, patients empty the bladder completely, discard this urine and drink 600 mL of distilled water. All urine produced during the next 2 hours is collected (fasting urine). A 1g oral calcium load is administered and urine is again collected over the next 4 hours (post-load urine). Both fasting and post-load samples are then assayed for calcium and creatinine.

This extensive evaluation can be time consuming, difficult, and expensive, since it requires multiple office visits and diet adherence. We do not routinely perform a calcium-loading test to differentiate between absorptive and renal leak hypercalciuria as the treatment of both

is similar. However, if the physician plans to prescribe a calcium-binding agent (sodium cellulose phosphate, orthophosphate), it may be beneficial to perform the test. Several authors have suggested more simplified protocols that do not include the calcium fast and loading tests and can be performed in 1 office visit. Some have recommended the collection of 2 separate 24-hour urine specimens, while others have advocated 1 24-hour random urine sample.[11] However, the adequacy of a single 24-hour urine evaluation has been challenged.[12]

THE 24-HOUR URINE EVALUATION

The urinary parameters typically assayed in the 24-hour urine evaluation include calcium, oxalate, citrate, total volume, sodium, magnesium, phosphate, potassium, pH, uric acid, and cystine. The normal values are shown in Table 4. Commercially available systems provide collection containers with chemical preservatives (obviating iced storage and refrigerated transport), and extrapolate 24-hour cumulative data from the submission of a small aliquot of the entire collection. The physician receives a report that provides a numeric and graphic display of the test results. Results display 24-hour excretion of urinary constituents along with supersaturation values for common urinary crystals. Urine supersaturation values have been shown to correlate well with the stone analysis and treatment outcomes.[13]

Using a 24-hour urine evaluation, patients with nephrolithiasis can be classified into 12 categories reflecting specific physiologic derangements (Table 5). However, 3% of all patients undergoing a full metabolic evaluation will demonstrate no abnormalities.[10] The potential reasons for having an error in 24-hour urine evaluation include error in collection technique, changes in the patient's diet, failure of specimen to accurately represent a "typical" day, and bacterial contamination.

Risk Factors for Recurrent Stone Disease

Multiple risk factors have been associated with recurrent nephrolithiasis. They are summarized in Table 2. Identifying a familial incidence of stones is useful. Geographic and occupational factors, medical conditions, and drugs are associated with recurrent stones. Certain stone types are also associated with recurrence. Anatomic factors associated with stasis are associated with recurrent stones as well.

Table 2. Risk Factors for Recurrent Nephrolithiasis

Demographic Factors
Male gender
Children
Family history of stone disease
Obesity
Geographic factors: residence in stone belt
Genetic Disorders
Cystinuria
Primary hyperoxaluria
Renal tubular acidosis
Xanthinuria
Stone Type
Uric acid stones
Cystine stones
Infection stones
Brushite stones
Bilateral stones
Staghorn calculi
Multiple stones
Recurrent calculi
Anatomic Factors
Medullary sponge kidney
Solitary kidney
Polycystic kidney disease
Nephrocalcinosis
UPJ (ureteropelvic junction) obstruction
Horseshoe kidney
Caliceal diverticulum
Hydronephrosis
Medical Diseases
Gastrointestinal disease (colitis, crohn's disease, malabsorption)
Hyperparathyroidism
Hyperthyroidism
Immobilization
Sarcoidosis
Osteoporosis
Gout
Medication-induced stones (indinavir, acetazolamide, triamterene, topiramate, ephedrine)

CONSERVATIVE MEASURES FOR PREVENTION OF RECURRENT NEPHROLITHIASIS

General recommendations should be made for all patients, regardless of the underlying cause of the stone disease and metabolic abnormality. After a few months of conservative management, patients should be re-evaluated. If the metabolic abnormalities have been corrected, conservative therapy can be continued. However, if the metabolic abnormalities persist, a more selective medical therapy should be instituted.

Fluid Intake

Low urinary volume is the most common abnormality (50% combined occurrence) seen on evaluation of

Table 3. Extensive Evaluation of High-risk, First-time, or Recurrent Stone Formers

	Blood				Urine							
	SMA	PTH	Calcium	Uric Acid	Calcium	Creatinine	Volume	Oxalate	Citrate	Volume	Oxalate	Cystine
Visit 1	X	X	X	X	X	X	X	X	X	X	X	X
Visit 2		X	X	X	X	X	X	X	X	X	X	
Fast					X	X						
Load					X	X						

SMA = Spinal muscular atrophy, PTH = Parathyroid hormone

Table 4. Normal Concentration of Urinary Constituents in 24-hour Urine Specimen

Urinary Constituent	24-hour Urinary Concentration
Calcium	<250 mg
Oxalate	<45 mg
Citrate	>320 mg
Magnesium	>60 mg
Phosphate	<1100 mg
Uric acid	<700 mg
Cystine	<250 mg
Urine volume	>2000 ml
pH	5.5-7.0

patients with nephrolithiasis.[10] Low urine volume can result from environmental factors such as inadequate fluid intake and dehydration, and also from malabsorptive bowel disorders that result in excessive fecal fluid losses. A consistently high fluid intake is the most effective means of reducing urinary supersaturation,[9] and failure to increase urine output is 1 of 3 strong predictors of relapse observed in a dedicated stone clinic.[14] A daily urine output >2 L is targeted. This can be accomplished by drinking more than 2.5 L/day, distributed throughout the day. At least 8-10 ounces of fluid should be ingested at bedtime, because urinary concentration usually occurs during sleep. A larger amount of fluids must be consumed if there is excessive sweating, diarrhea, or vomiting, and in patients whose urinary risk factors cannot be satisfactorily controlled with targeted nutrition therapy and/or pharmacologic therapy. In these patients, higher urine output—exceeding the 2 L/day cutoff—is necessary to maintain suitably low urinary supersaturation in the face of a high concentration of crystal promoters. Similarly, patients on medications known to increase risk for urinary stones should be advised to aim for a higher urine output.

Although water hardness can alter urinary parameters, it appears to have little effect on clinical outcomes. Carbonated water has been shown to protect against recurrent stone formation.[15] Epidemiologic studies have demonstrated that people who consumed high volumes of water, caffeinated or decaffeinated coffee, tea, beer, and wine have a decreased risk of nephrolithiasis.[16] In those with suboptimal dietary calcium intakes, consumption of caffeinated beverages should be limited to offset the modest hypercalciuric effect of caffeine.[17]

Animal Protein and Acid-base Balance of Diet

Dietary protein of animal origin provides an acid load to the body; increases urinary calcium, oxalate, and uric acid excretion; reduces citrate excretion and urinary pH; and increases probability of stone formation, even in normal subjects.[18-19] Animal protein restriction has been shown to decrease urinary calcium, phosphate, uric acid, and oxalate excretion.[20] Strategies to accomplish a reduction in animal protein intake include reduced portion sizes as well as reduced frequency of intake throughout the week.

In all stone-forming patients, we recommend a diet rich in fruits and vegetables (>5 servings/day). The potassium content of these foods will counteract the high acid load of the typical Western diet. Additionally, fruits and vegetables provide other nutrients and compounds that are associated with reduced stone risk,[21] including magnesium, phytate, fiber, citric acid, and many non-nutrient antioxidants.

Oxalate

Reduced oxalate intake is recommended for patients with hyperoxaluria. Foods known to cause a high urinary excretion of oxalate include tea (both green and black), nuts, chocolate and cocoa, spinach, beets, rhubarb, and soybeans and soy foods (eg, tofu).[22-23] Dietary fat intake should be reduced since fat may enhance oxalate absorption.[24] Vitamin C supplementation should be restricted to <1000 mg/day, if at all, as it is metabolized to oxalate.[25] Other nutritional supplements, such as cranberry tablets[26] and supplements containing concentrated plant derivatives may confer a high oxalate load and should be avoided. Recently, a study in calcium oxalate stone formers revealed that a subset developed hyperoxaluria as a result of a high meat intake.[27] The role of meat intake in the development of hyperoxaluria

Table 5. Classification of Patients Based on 24-hour Urine Evaluation

	Ca	P	PTH	Ca Fasting	Ca Load	Ca Restricted	UA	Ox	Cit	pH	Mg
Absorptive hypercalciuria type 1	N	N	N	N	↑	↑	N	N	N	N	N
Absorptive hypercalciuria type 2	N	N	N	N	↑	N	N	N	N	N	N
Renal hypercalciuria	N	N	↑	↑	↑	↑	N	N	N	N	N
Primary hyperparathyroidism	↑	↓	↑	↑	↑	↑	N	N	N	N	N
Unclassified hypercalciuria	N	N/↓	N	↑	↑	↑	N	N	N	N	N
Hyperuricosuria	N	N	N	N	N	N	↑	N	N	N	N
Enteric hyperoxaluria	N/↓	N/↓	N/↓	↓	↓	↓	↓	↑	↓	N	N
Hypocitraturia	N	N	N	N	N	N	N	N	↓	N	N
Renal tubular acidosis	N	N	N/↑	↑	N	N/↑	N	N	↓	N/↑	N
Hypomagnesiuria	N	N	N	N	N	N	N/↓	N	↓	N	↓
Gouty diathesis	N	N	N	N	N	N	N/↑	N	N/↓	↓	N
Infection lithiasis	N	N	N	N	N	N	N	N	↓	↑	N

Ca = Calcium, P = Phosphorus, PTH = Parathyroid hormone, UA = Urinalysis, Ox = Oxalate, Cit = Citrate, Mg = Magnesium.
N = Norrmal, ↑ = Increased, ↓ = Decreased.

warrants further attention.

Patients in whom hyperoxaluria cannot be controlled with dietary oxalate restriction and those with enteric hyperoxaluria should be managed by optimizing calcium intake. This can be done by ensuring they meet the adequate intake (AI) for calcium (between 1000-1200 mg/day for adults) and that it is distributed throughout the day with meals. Calcium acts by binding with oxalate in the gastrointestinal tract, forming an insoluble complex.

Calcium

In 1 prospective study, dietary calcium was inversely associated with the risk of kidney stones.[28] However, similar results were not seen with calcium supplementation.[29] Thus, a normal calcium intake from foods may be continued per the AI in almost all stone forming patients. A severe calcium restriction may increase oxalate absorption, thereby raising the supersaturation of calcium oxalate.[28-29] Calcium supplementation should be considered mainly in those whose dietary calcium is suboptimal and in enteric hyperoxaluria.[30]

Sodium

Dietary sodium has been shown to increase urinary calcium and pH and decrease citrate excretion. In a prospective, randomized study, Borghi and colleagues demonstrated that patients on a low-animal protein (52 g/day), low-sodium (1150 mg/day), and moderate-calcium (1200 mg/day) diet had a 50% reduction in stone events compared to those on a low-calcium (400 mg/day) diet.[31] Sodium intake should be restricted in all stone formers to <200 mEq (4600 mg)/day and even less in those with hypercalciuria. The Estimated Safe and Adequate Daily Dietary Intake range for sodium, determined to meet the needs of most healthy adults, is 1100-3300 mg/day. We believe in aggressive nutrition counseling to identify foods contributing most to sodium intake as sodium added to foods, either during cooking or at the table, accounts for far less than half of total sodium intake among Americans.[32] As sodium counteracts the ability of thiazide to control hypercalciuria, patients on this therapy especially should be counseled about sodium restriction.

Dietary Citrate

Specific fruits and fruit juices are rich sources of citric acid. The juice of lemons and limes are most concentrated with citric acid. Other fruit juices like orange, grapefruit, apple, and black currant juice contain appreciable citric acid as well and may also increase urinary citrate by providing an alkali load. However, orange, grapefruit, and black currant juice also raise urinary oxalate,[33-34] potentially offsetting the crystal inhibitory effect of the citric acid. Moreover, fruit juices generally provide ample carbohydrate and kilocalories, excessive intake of which should be avoided to maintain appropriate weight. In all patients forming calcium stones, we consider "lemonade therapy," consisting of 4 ozs/day of lemon or lime juice—either squeezed from the fresh fruit or in their concentrated forms—providing about 6 g of citric acid.[35] Alternatively, 32 ozs/day of a low-sugar, low-calorie lemonade or limeade product provides a similar amount of citric acid and has the added benefit of adding to total fluid intake, enhancing urine volume and reducing urinary supersaturation of crystalloids. This therapy does not replace the need for the alkali load delivered by ample fruits and vegetables.

Obesity

Obesity is an independent risk factor for urinary calculi, especially in women.[36] Obese patients are known to have

increased urinary excretion of sodium, calcium, sulfate, phosphate, oxalate, uric acid, and cystine, and also likely to have a more acidic urine, which may explain the increased incidence of uric acid calculi. Although obese patients should be advised to lose weight, certain weight-reduction diets should be avoided, particularly those such as the Atkins diet (which is low-carbohydrate, high-protein, and high-fat), which delivers a marked acid load to the kidney, further increasing the risk for stone formation and bone loss.[37]

SELECTIVE MEDICAL THERAPY FOR RECURRENT NEPHROLITHIASIS

If physiochemical aberrations are seen on the 24-hour urine evaluation, selective medical therapy can be instituted to correct these disturbances and prevent future stone formation. The commonly used medications, their indications, doses, and side effects are listed in Table 6.

Absorptive Hypercalciuria

No medical treatment is capable of correcting the basic abnormality of absorptive hypercalciuria type 1. Due to their cost-effectiveness and lower incidence of side effects, thiazides may be utilized as first-line therapy. Appropriate dietary restriction of calcium and oxalate, combined with thiazide and potassium citrate, can decrease the stone formation rate from 2.94 to 0.05 per year.[38] However, thiazides may have limited long-term effectiveness in this condition.[39] About 30%-35% of patients on thiazides will experience side effects, most of which are mild in nature. Although sodium cellulose phosphate can reduce the stone events by 78%,[40] it is associated with an extremely high rate of gastrointestinal distress. Its use should be restricted only to patients with severe absorptive hypercalciuria type 1 who are resistant to or intolerant of thiazide therapy.

Patients on this medication should be on a low-oxalate diet and supplemented with magnesium since magnesium depletion can occur due to the binding of magnesium and secondary hyperoxaluria can occur due to the binding of divalent cations in the intestinal tract.[40] Orthophosphates have been shown to inhibit 1,25-dihydroxyvitamin D synthesis,[41] decrease urinary calcium, and increase urinary citrate and phosphate.[42] However, there is no convincing evidence that this treatment restores normal intestinal calcium absorption in absorptive hypercalciuria type 1. It may be specifically indicated in absorptive hypercalciuria type 3 (vitamin D dependent). We do not routinely use sodium cellulose phosphate or orthophosphates for management of absorptive hypercalciuria in our metabolic stone clinic.

Patients with absorptive hypercalciuria type 2 can be managed conservatively with a normal calcium intake, high fiber diet, and high fluid intake. No specific drug treatment may be necessary since the physiologic defect is not as severe as in absorptive hypercalciuria type 1.

Renal Hypercalciuria

Thiazide diuretics are the treatment of choice for renal hypercalciuria as they correct the renal leak of calcium by augmenting calcium reabsorption in the distal tubule. With prolonged therapy, they cause extracellular volume depletion, which leads to stimulation of proximal tubular reabsorption of calcium. Long-term efficacy has been reported.[39] To avoid hypokalemia, patients on thiazides should be either supplemented with potassium citrate or started on a potassium-sparing diuretic like amiloride.

Resorptive Hypercalciuria

Resorptive hypercalciuria is an infrequent abnormality commonly associated with primary hyperparathyroidism. Primary hyperparathyroidism is the most common cause of hypercalcemia in an outpatient setting, and is associated with nephrolithiasis in <5% of affected individuals.[43] However, the diagnosis should be suspected in patients with nephrolithiasis and serum calcium levels >10.1 mg/dL. An assay for intact PTH can help distinguish patients with hyperparathyroidism from those with other causes of hypercalcemia. Parathyroidectomy is the treatment of choice for patients with primary hyperparathyroidism and nephrolithiasis.

Hyperuricosuric Calcium Oxalate Nephrolithiasis

Patients with hyperuricosuric calcium oxalate nephrolithiasis have monosodium urate-induced calcium oxalate crystallization. Hyperuricosuria associated with dietary purine overindulgence (purine gluttony) may be treated with dietary purine restriction. Patients with refractory disease can be treated with allopurinol or by urinary alkalanization with potassium citrate. In a double-blinded, prospective, randomized, controlled trial, allopurinol was shown to have a stone formation rate of 0.12 per patient per year compared to 0.26 in the placebo group.[44] Similarly, in another study, potassium citrate decreased stone formation from 1.55 to 0.38 per patient-year during a mean treatment period of 2.35 years.[45] Potassium citrate may be particularly useful in patients with mild to moderate hyperuricosuria (<800 mg/day), especially if hypocitraturia is also present.

Enteric Hyperoxaluria

Oral administration of large amounts of calcium or magnesium, taken with meals, should be recommended

Table 6. Common Medications Used for Medical Management of Urinary Calculi

Medication	Indications	Mechanism of Action	Dose	Side-effects
Thiazide diuretics Hydrochlorothiazide Chlorthalidone Indapamide	Hypercalciuria (all causes)	Stimulates calcium resorption in the distal nephron, prolonged therapy results in volume depletion and proximal tubular resorption of calcium	25 mg bid 25-50 mg daily 2.5 mg daily	Potassium wasting, muscle cramps, hyperuricosuria, intracellular acidosis, hypocitraturia, umasking of hyperparathyroidism, sexual dysfunction
Sodium cellulose phosphate	Severe absorptive hypercalciuria	Binds intestinal calcium and inhibits absorption	10-15 g/day divided with meals	Gastrointestinal distress, hyperoxaluria, hypomagnesemia, parathyroid hormone stimulation
Orthophosphate	Absorptive hypercalciuria	Inhibits vitamin D synthesis, impairs renal tubular reabsorption of calcium, binds calcium in the GI tract, increase urinary pyrophosphate	0.5 g tid	Similar to sodium cellulose phosphate, soft tissue calcification, brushite stone formation
Potassium citrate	Thiazide therapy, hypocitraturia, hyperuricosuria, gouty diathesis, cystinuria, enteric hyperoxaluria	Increases urinary citrate and pH, decreases urinary calcium. Corrects metabolic acidosis and supplements potassium	20 mEq bid-tid	Gastrointestinal upset, hyperkalemia
Allopurinol	Hyperuricosuria, gouty diathesis	Inhibits xanthine oxidase which converts xanthine to uric acid, thus decreasing serum and urine uric acid levels	300 mg daily	Rash, myalgia
Magnesium	Hypomagnesuria, adjunct to sodium cellulose phospate	Increases urinary magnesium and citrate, decreases urinary oxalate	0.5-1.0 g tid	Diarrhea
D-Penicillamine	Refractory cystinuria	Chelates cystine	250 mg daily (titrate to effect)	Nephrotic syndrome, dermatitis, pancytopenia
α-mercaptopropionyl glycine	Cystinuria	Chelates cystine	100 mg bid (titrate to effect)	Rash, asthenia, GI distress, rheumatologic complaints, mental status changes
Captopril	Cystinuria	Chelates cystine	25 mg bid-tid	Rash, cough, hypotension
Acetohydroxamic acid	Infection stones	Inhibits urease and reduces the urine saturation of struvite	250 mg bid-tid	Thromboembolism, tremor, headache, palpitations, GI distress, loss of taste, rash, alopecia, anemia, edema, abdominal pain

Bid=2 times per day; Tid=3 times per day; GI=gastrointestinal.

to prevent oxalate absorption from foods.[30] However, the concurrent rise in urinary calcium may occasionally obviate the beneficial effect of this therapy. Calcium citrate may be the optimum salt as it may raise urinary citrate excretion and urine pH.[46] Cholestyramine may be used as well because it binds bile salts in the bowel lumen, thereby decreasing the irritation of the colonic mucosa and the subsequent hyperabsorption of oxalate.[47] Magnesium gluconate should be given to patients with hypomagnesuria from chronic malabsorption because it is better tolerated than other magnesium products. Potassium citrate may correct the hypokalemia and metabolic acidosis associated with severe enteric hyperoxaluria. The liquid form of this medication should be used because it is better absorbed than the slow-release, wax matrix pills. A high fluid intake and an antidiarrheal agent may be necessary to ensure adequate urine volume. Dietary modifications include decreasing dietary fat and oxalate intake.

Hypocitraturic Calcium Oxalate Nephrolithiasis

Hypocitraturia is a common metabolic abnormality seen in 50% of patients with nephrolithiasis.[10] Hypocitraturia from distal renal tubular acidosis can be managed with potassium citrate therapy, which is capable of correcting the metabolic acidosis and hypokalemia and restoring normal urinary citrate levels in larger doses (up to 120 mEq/day). Potassium citrate can also be utilized for treatment of hypocitraturia due to chronic diarrheal states, thiazide therapy, and idiopathic hypocitraturia. Citrate supplementation with lemonade[35] and orange juice[33] has also been shown to increase urinary citrate excretion.

Hypomagnesiuric Calcium Nephrolithiasis

Hypomagnesiuric calcium nephrolithiasis is characterized by low urinary magnesium level, hypocitraturia, and low urine volume. Management includes increasing urinary magnesium levels with a magnesium salt and correction of the hypocitraturia with potassium citrate. Magnesium oxide and magnesium hydroxide are the mostly commonly used form of magnesium. Both are poorly absorbed and produce only a slight decrease in urinary oxalate and a modest increase in urinary magnesium. Urinary calcium and citrate levels are increased during magnesium oxide supplementation,[48] and thus urine saturation of calcium oxalate is not significantly lowered.

Older studies have shown that magnesium therapy is associated with decreased stone recurrence. Ettinger reported a double-blinded, randomized trial of potassium-magnesium citrate versus placebo and showed that 12.9% versus 63.6%, respectively, developed calculi.[49] However, this product is currently not available for use in the United States.

Gouty Diathesis

The most common metabolic abnormality in patients with uric-acid stones is not hyperuricosuria, but increased urinary acidity followed by low urinary volume. These patients should be managed with hydration and potassium citrate at a dose sufficient to maintain urine pH of approximately 6.5. Attempts at alkalinization to a pH higher than 7.0 should be avoided because it is associated with an increased risk of calcium phosphate stone formation. If the urinary uric acid excretion is persistently elevated or hyperuricemia exists, allopurinol (300 mg/day) should be added. Allopurinol is also preferred in patients with marked hyperuricosuria (>1000 mg/day).

Cystinuria

The goal of treatment of cystinuria is to keep the urine concentration of cystine below its solubility limit (200 to 300 mg/L). This can be done initially by increasing the urine volume by high fluid intake. Dietary manipulation with a low-methionine diet is rarely successful; however, dietary sodium should be restricted since it can lead to increased urinary cystine excretion.[50] Solubility of cystine can be increased to 400 mg/L by alkalinizing the urine with potassium citrate to a pH of 7.0. Further alkalinization up to the pKa of cystine (8.3) can be difficult and risky. Failure of these conservative measures requires therapy with chelating agents, which have a sulfhydryl group that forms a disulfide bond with cystine (cysteine). Due to better tolerability, α-mercaptopropionylglycine is preferred over D-penicillamine. Captopril can be used as well; however, there are no long-term clinical trials demonstrating its effectiveness.

Infection Stones

Complete surgical removal of all infected stone material is essential for the prevention of recurrent struvite stone formation. Long-standing effective control of infection can be achieved by preventing bladder infections, achieving adequate urine drainage, and appropriate use of suppressive antibiotics. Although acetohydroxamic acid can effectively inhibit urease, its use should be reserved for patients who are not candidates for surgery because of the risk of serious side effects.

SUMMARY

All urolithiasis patients should undergo a basic evalua-

tion in order to rule out treatable systemic causes. All recurrent stone formers should have a more extensive metabolic evaluation based on 24-hour urine samples. A significant number of patients may be able to normalize their urinary risk factors using conservative, nonspecific preventive measures. Selective medical therapy tailored to the individual patient's metabolic evaluation is effective in preventing new stone formation. However, continued compliance of patients and a commitment by the physician to provide long-term follow-up and care are vital.

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Leonard W. Barry, MS

Seven key questions to ask when choosing a financial advisor

Leonard W. Barry, MS

If you prefer to delegate the management of your investment portfolio rather than do it yourself, it is wise to choose your financial advisor carefully. Your advisor must be someone you can trust to manage your money and look out for your interests, now and in the future.

Consider the following questions when choosing a financial advisor:

What services do you offer?
The best financial advisors take a broad approach to your financial situation. Look for an advisor who offers comprehensive financial planning in addition to investment counseling and asset management services. Comprehensive planning can include advice on areas such as retirement planning, education funding, charitable giving, insurance, taxes, and estate planning.

What credentials do you hold?
Anyone can use the title "financial advisor" or "financial planner." Consumers can rely on credentials to help assess a financial advisor's qualifications. The following are common reputable credentials:

- A Certified Financial Planner® has demonstrated educational knowledge of the major components of financial planning, passed a comprehensive examination, satisfied a work experience requirement, and agreed to adhere to a code of ethics.
- A Chartered Financial Analyst has completed a rigorous self-study graduate-level program in investments and portfolio management, passed 3 examinations, satisfied a work experience requirement, and agreed to adhere to a code of ethics.
- A Chartered Financial Consultant® has completed courses in the major components of financial planning and satisfied a work experience requirement.
- A graduate degree in a field such as finance, economics, financial planning, or business administration can signify knowledge relevant to assisting clients with financial planning and investment management.

How are you compensated?
There are 3 main ways financial advisors get paid: commissions only, a combination of commissions and fees, or fees only. You should understand how your advisor is compensated, because this could create a conflict of interest. An advisor who receives commissions may have an incentive to use investments that are more lucrative for the advisor. By contrast, a "fee-only" advisor does not receive any type of commission from the investments he or she recommends.

It is also important to understand what commissions or charges, if any, are associated with the investment products your advisor uses. These commissions or charges may directly or indirectly compensate the advisor or the advisor's firm. For example, many advisors use mutual funds because they are an effective way to diversify an investment portfolio. Some mutual funds are "no-load," which means there is no up-front or deferred charge to buy the fund. Other mutual funds charge an up-front fee to buy, or a deferred fee if you sell within a certain number of years. There are a variety of options when buying mutual funds, so ensure that you read the product's prospectus carefully and understand the product before investing.

Do you have a fiduciary responsibility to your clients?
Fiduciary responsibility means the advisor is legally obligated to act in the client's best interest. This is true of advisors who work for firms that are Registered Investment Advisors. It is also true of Certified Public Accountants (CPAs) and attorneys. The investing public generally does not realize that other professionals may not be legally obligated to act in the client's best interest. On the other hand, many professionals belong to, or are regulated by, professional associations that impose standards for ethical practice.

Leonard W. Barry holds a master's degree in personal financial planning. He is a financial consultant for SVA Wealth Management, Inc., Registered Investment Advisor, an affiliated company of Suby, Von Haden & Associates, S.C. He specializes in comprehensive financial planning and investment management. For more information contact Wisconsin Medical Society Insurance and Financial Services, Inc. toll free at 866.442.3810.

What experience do you have?
In addition to formal education and credentials, what is the advisor's professional experience? Does this advisor have a proven track record? If the advisor appears less experienced, what are the firm's policies for mentoring and supervising financial advisors?

Look for an advisor who is affiliated with a firm that has established processes and a shared investment philosophy. How are investment decisions made? It is a good sign if a firm has a disciplined investment approach that all of its advisors follow.

How will you report the performance of my investment portfolio?

There should be no mystery about the performance of your investments. You should expect regular reports in an easy-to-understand format that shows the portfo lio performance, net of all fees. Request a sample report and ask the advisor to walk you through it.

What is your disciplinary history?
The financial professions are highly regulated. If a financial advisor has been disciplined, he or she should be willing to explain the source and result of the action. You can check the advisor's disciplinary history by contacting the following organizations:

- The North American Securities Administrators Association, 202.737.0900, www.nasaa.org
- The Financial Industry Regulatory Authority, 800.289.9999, www.finra.org
- The National Association of Insurance Commissioners, 816.842.3600, www.naic.org

Conclusion
A comfortable retirement, higher education for your children or grandchildren, travel, a vacation home, charitable gifts, a legacy for your family—whatever your goals are—keep in mind that money is merely a means to an end. Look for a financial advisor who puts your interests first.

Michael J. Dunn, MD

Dean's Corner

Efforts in pharmacogenetics will help patients get right amount of right drug

Michael J. Dunn, MD
Dean and Executive Vice President, Medical College of Wisconsin

Physicians know that some patients respond better to one drug than another, despite the drugs having identical mechanisms of action. They also know that a beneficial drug can be either harmful or useless if the dose is too high or too low. From these simple observations, the surprisingly mature field of pharmacogenetics originated.

Since at least the 1950s, this information has been documented and to some extent utilized to make clinical decisions, but with the advent of the Humane Genome Project, pharmacogenetics has raced to the forefront of medicine as researchers elucidate the substantial role of genes in the body's interaction with drugs. As we recognize the vast potential of this knowledge to improve outcomes, the Medical College of Wisconsin has faculty physicians and scientists dedicated to answering key questions that will make drug development and use safer and more effective.

In practical application, pharmacogenetics uses a genetic assessment to predict a patient's response to a pharmaceutical treatment. For the patient, it individualizes treatment to the extent that optimal therapy may be achieved more quickly and toxicity may be avoided. The most dramatic influence may be for those drugs that have a narrow therapeutic window—the distance in drug concentration between what is therapeutic and what is toxic. When drugs have a wide therapeutic window, refining the dose is not as important. When the window is narrow, precise dosing is crucial.

The anticoagulant warfarin is an apt example and one in which pharmacogenetics has changed the way the drug is prescribed. While the drug is not new, recent research into the 2 genes that account for the majority of the variation seen in human response to the drug has resulted in algorithms physicians can use. These algorithms take into account the patient's gender, age, body mass, and the genetics of 2 different gene loci: 1 for the enzyme that is involved in metabolism of the drug (CYP2C9) and 1 for the target (VKORC1), the enzyme that gets blocked by warfarin. The result is a recommended starting dose optimized for that patient.

Chemotherapy drugs also have a narrow therapeutic window, so pharmacogenetics is helping patients avoid toxicity from drugs such as thiopurine methyltransferase (TPMT). People who are homozygous for the variant in the gene that handles TPMT have a much greater risk of adverse outcomes.

Such variants underscore the importance of a pharmacogenetic approach to patient care. Researchers have discovered that many of the genetic variants that affect drug response and drug disposition in the body are relatively common. Some exist in 40%—50% of the population. Now, the challenge is to build on the plethora of knowledge that is the foundation of the field. In many cases, we know which enzymes handle which drugs, we are aware of the polymorphisms that contribute to varied response, and we generally know how much of an impact these variations have. By working to expand the science, we facilitate the development of tools or other resources that physicians can use.

Ron Hines, PhD, and Gail McCarver, MD, are among the most active Medical College of Wisconsin investigators in pharmacogenetics. Dr Hines is professor and Dr McCarver is associate professor of Pediatrics and of Pharmacology/Toxicology. They are Pediatric Co-section Chiefs of Clinical Pharmacology, Pharmacogenetics and Teratology, and they conduct much of their work within the Children's Research Institute.

Pharmacogenetics in the pediatric population has distinctive elements, particularly in that different genes turn on (and off) at different times in human development. Some genes may turn on prior to birth. Others may turn off at birth. Even more may be silent until a child is 1 or 2 years old. The combinations are nearly endless and mean that the enzymes that handle different drugs may or may not be functioning depending on age.

A major area of research for Dr Hines centers on the liver, which, of all organs in the body, has the greatest concentration of drug metabolizing enzymes. He has sought to identify when genes turn on and begin producing drug metabolizing enzymes, as well as how this might affect response to therapy or adverse reactions.

His team quickly discovered tremendous variability, not just from gene to gene, but also person to person. Now, they are concentrating not only on mapping out when different genes in the liver system turn on in individuals, but also examining what could be regulating that variability.

Dr Hines' group also has a National Institutes of Health subcontract with one of the pioneers in the field who actually discovered the genetic variation on CYP2C9 that impacts warfarin, Allan Rettie, PhD, at the University of Washington. The Medical College team is focusing on an African American population of patients at Froedtert Hospital. As a demographic, African Americans require a higher average dose of warfarin than do Caucasians. (For that matter, Caucasians require higher doses than Asians, and children at an early age require higher doses than adults). The research hopefully will explain what causes these differences.

Doctor McCarver is heading a number of projects at the basic science level, some of which overlap into the field of toxicogenetics. For example, she is studying how a particular enzyme handles chlorzoxazone, a muscle relaxant. The research is looking at the compound in the context of both alcohol and solvents in the environment while considering specific genetic polymorphisms and how they interrelate to exposure, and how the two together relate to outcomes of infants of women who were exposed during pregnancy. Further pharmacogenetics research is aimed at how that enzyme is regulated. Doctor McCarver also has a project looking at methadone metabolism in infants and the genetic factors, in conjunction with age, that influence it.

Other faculty members in the section have research dedicated to genetics' effect on the proteins that transfer thiopurines in and out of cells as well as the pharmacogenetics of pain management.

Together, Dr Hines and Dr McCarver are leading a pharmacogenetics initiative expected to roll out in July. The clinical protocol will be a pilot in Children's Hospital of Wisconsin's First-time Seizure Clinic. Using a gene chip—a piece of technology that contains information on 150-200 different genes—every child admitted to the clinic will have his or her genes tested. The patient's genetic make-up should help doctors decide what particular drug will be best for the child for seizure control and what dose might be optimal.

The clinic admits approximately 400 children a year who have had a seizure for the first time. Since the drugs used for seizure control have a high adverse toxicity rate, choosing the best drug and dose is very important. The project unites the genetic expertise of Uli Broeckel, MD, associate professor of Medicine, and David P. Bick, MD, associate professor of Pediatrics, both researchers in the Medical College's Human and Molecular Genetics Center, with the neuropharmacology knowledge of Charles J. Marcuccilli, MD, PhD, assistant professor of Pediatric Neurology at the Medical College.

As more investigations take place, practicing physicians will be challenged to keep current and make use of the resulting information. Most important, according to Dr McCarver, will be a physician's knowledge of clinical pharmacology; for example, what enzyme handles a drug, whether the drug is inactivated or activated by metabolism, and what receptor in the body is involved. We expect the materialization of more Web sites and searchable databases that list such information, but clinicians will need to understand the concepts to make use of the tools.

Of course, pharmacogenetics is just a piece of a larger landscape that aids in diagnoses and treatment. Age, diet, and interaction with other medications are all confounding factors that must be considered if pharmacogenetics is to be used successfully in clinics. The more our studies uncover, however, the more we realize that pharmacogenetics is an opportunity to improve outcomes in virtually all disease areas, and that is worth our full attention.

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